Table 4.6 Cytogenetic changes in humans exposed to benzene

Description of exposed and controls	Exposure duration (years)	Exposure in air (ppm)[a]	Cytogenetic changes[b]	Comments	Reference
Woman (age, 38 yr) with benzene-induced leukaemia (case study)			+ for extra chromosomes, mostly in C group (group C trisomy)	All chromosomes	Forni & Moreo (1967)
Woman (age, 37 yr) with benzene-induced acute erythroleukaemia (case study)			+ for cytogenetic changes	All chromosomes	Forni & Moreo (1969)
5 women with benzene haemopathy, diagnosed 5 yr previously, 1 control	NR	NR	+	% aneuploid lymphocytes (40%) decreased from time of diagnosis (70%)	Pollini et al. (1969)
4 women with benzene myelopathy diagnosed 10 yr previously, 1 control	NR	NR	Same subjects as Pollini et al. (1969)	All had lower % aneuploid cells than control	Pollini et al. (1976)
4 women with benzene myelopathy diagnosed 12 yr previously, 1 control	NR	NR	Same subjects as Pollini et al. (1969)	All had lower % aneuploid cells than at previous follow-ups, but closer to control	Pollini & Biscaldi (1977)
33 workers exposed to benzene, 15 general-population controls; all smokers	10–23	< 31.3	+ for structural CAs In exposed workers, chromosomes 2, 4, and 9 almost twice as susceptible to breaks; 1 and 2 almost twice as susceptible to gaps; chromosome 18 underrepresented for CAs In unexposed controls, more random distribution of the breakpoints	All chromosomes	Sasiadek et al. (1989)
56 workers in plants, 20 controls	10–20 (not clearly defined)	< 10	+ for structural CAs (mainly breaks and gaps) and non-random distribution of breakpoints, which accumulated mainly on chromosomes 2, 4, and 7	All chromosomes	Sasiadek (1992)
58 shoemakers, 20 general-population controls	5–50	NR	(+) for polyploidy	All chromosomes	Tunca & Egeli (1996)
18 petrochemical workers (benzene plant or coke oven workers), 15 controls (including some office workers)	NR	Benzene plant, 1.1 (mean) Coke oven, 0.04 (mean) (8-h TWA)	– for chromosome 9 numerical abnormalities	Chromosome 9; buccal cells	Surrallés et al. (1997)

Table 4.6 (continued)

Description of exposed and controls	Exposure duration (years)	Exposure in air (ppm)[a]	Cytogenetic changes[b]	Comments	Reference
43 Chinese factory workers, 44 other factory controls	0.7–16 (mean, 6.3)	1–328 (median, 31) (8-h TWA, based on geometric mean of five 8-h measures)	+ dr for hypo- and hyperdiploidy of chromosome 8; hyperdiploidy of chromosome 21; t(8,21), t(8;?), t(21,?), and chromosome 8 breaks but not deletions	Chromosomes 8 and 21; same study population as some Zhang et al. studies (2007 and others), different chromosomes evaluated	Smith et al. (1998)
43 Chinese factory workers, 44 factory controls	0.7–16.0 (mean, 6.3)	1–328 (median, 31) (8-h TWA, based on geometric mean of five 8-h measures)	+ dr for monosomy 5 and 7 but not 1; trisomy 1, 5, and 7; tetrasomy 1, 5, and 7; –5q; –7q; total structural CAs in 5 and 7 (+) for chromosome 1 breaks at the centromere	Chromosomes 1, 5, and 7; same study population as for some Zhang et al. studies (2007 and others), different chromosomes evaluated	Zhang et al. (1998a)
12 benzene factory workers, and 5 cokery workers; 17/8 rural village population controls	0.7–19 (GM, 4.1)	0.0–9.0 (GM, 0.41)	(+) for hyperploidy in both chromosomes 1 and 9 in cultured lymphocytes; (+) for chromosome 1 hyperploidy and breakages (9 not reported) in smear cells; + for breakages in chromosomes 1 and 9 in cultured lymphocytes	Chromosomes 1 and 9; blood smear granulocytes and lymphocytes, and stimulated (cultured) lymphocytes	Marcon et al. (1999)
5 cokery workers, 8 rural village population controls	0.5–30.6 (GM, 4.8)	0.16–0.53 (GM, 0.31)	(+) for hyperploidy in both chromosomes 1 and 9 in cultured lymphocytes		
43 Chinese factory workers, 44 factory controls	0.7–16 (mean, 6.3)	1–328 (median, 31) (8-h TWA, based on geometric mean of five 8-h measures)	+ dr for monosomy (one hybridization signal) 7 and 8 in metaphase but not interphase + dr for trisomy (3 hybridization signals) 7 and 8 in metaphase and interphase, but more pronounced in metaphase	Chromosomes 7 and 8; same study population as for other Zhang et al. studies (e.g. 2007), different chromosomes evaluated; compared sensitivity of metaphase and interphase FISH, metaphase more sensitive	Zhang et al. (1999)
44 Chinese workers, 44 controls	NR	1.6–328.5 (median, 31)	(+) dr for hyperploidy in Ch chromosome 1	Chromosomes 1 and 9	Eastmond et al. (2001)
12 Estonian benzene production workers, 5 coke oven workers, 8 controls	Benzene workers, 6.6 (mean) Coke workers, 11.4 (mean)	Benzene workers, 4.1 (mean) Coke workers, 1.1 (mean)			

Table 4.6 (continued)

Description of exposed and controls	Exposure duration (years)	Exposure in air (ppm)[a]	Cytogenetic changes[b]	Comments	Reference
82 coke oven workers, 76 controls	0.75–19.67 (mean, 8)	0.014–0.743 (GM, 0.557) (8-h TWA)	+ for both monosomy and trisomy of both 8 and 21; + for t(8,21) translocations	Chromosomes 8 and 21	Kim et al. (2004b)
43 factory workers, 44 factory controls	0.7–16 (mean, 6.3) (from Smith et al., 1998)	1–328 (median, 31) (8-h TWA, based on geometric mean of five 8-h measures)	+ dr for monosomy and trisomy of all 7 chromosomes; + for exposed vs non-exposed for tetrasomy of all 7 chromosomes; some selectivity at lower exposures: only monosomy 6 and trisomy 4, 6, and 11 were + in the < 31 ppm group; + for –6q and t(14;18); – for t(4,11) and t(6,11)	Chromosomes 2, 4, 6, 11, 12, 14, and 18; same study population as for Smith et al. (1998) and other Zhang et al. studies, different chromosomes evaluated	Zhang et al. (2007)
57 Chinese factory workers exposed to benzene (20 low-dose and 37 high-dose), 31 unexposed factory workers (not clearly reported) Subset: 37 benzene-exposed workers, 20 unexposed factory workers (not clearly reported)	NR	Low, 1.8 (mean) High, 21.9 (mean) Subset, 22.6 (mean)	t(14,18) signif ↓d no t(8,21) observed 2 t(15,17), but 1 in unexposed, 1 in exposed	t(15;17) and t(8,21) t(14,18) in subset	McHale et al. (2008)
649 MDS cases, 80 with benzene exposure (13.2%), 29 highly exposed > 21 ppm	High, > 0.5 (mean, 12)	> 21	– *	–5/5q–, –7/7q–, +8, del(20q) and 11q23/*MLL* * – for benzene-exposed vs non-exposed MDS cases	Irons et al. (2010)
30 petroleum refinery workers, 10 office worker controls		0.51 (mean)	+ for chromosomes 7, 9 for aneuploidy	Chromosomes 7 and 9	Kim et al. (2010)
33 Chinese male factory workers using benzene-containing glues, 33 factory worker controls	> 1	< 0.2–23.6 (median, 2.9) (8-h TWA)	+ for disomy X and disomy Y; – for disomy 21	Chromosomes 21, X, and Y in sperm; same population as Ji et al. (2012) (PBL results)	Xing et al. (2010)
47 shoemakers (22 exposed to benzene at < 10 ppm, 25 at ≥ 10 ppm), 27 clothing factory controls	NR	Low, 4.95 (mean) High, 28.33 (mean) (Based on multiple samples over 3 mo)	+ selectivity; + dr for monosomy 5, 6, 7, 10, 16, and 19; + dr for trisomy 5, 6, 7, 8, 10, 14, 16, 21, and 22	All chromosomes; OctoChrome FISH: chromosome-wide aneuploidy study (CWAS)	Zhang et al. (2011)

Table 4.6 (continued)

Description of exposed and controls	Exposure duration (years)	Exposure in air (ppm)[a]	Cytogenetic changes[b]	Comments	Reference
33 Chinese male factory workers, 33 control factory workers	> 1	< 0.2–23.6 (median, 2.9) (8-h TWA)	(+) for trisomy 21; – for gain X and gain Y	Chromosomes 21, X, and Y; same population as Xing et al. (2010) (sperm results)	Ji et al. (2012)
30 workers in China who used benzene-containing glues, 11 factory worker controls	> 1–NR	< LOD–23.6 (GM, 2.8)	(+) for disomy 1	Chromosome 1 in sperm	Marchetti et al. (2012)
Man (age, 43 yr) with MDS and AML (case study)	16 (HQ)		+ CAs in chromosomes 5 and 7		Regev et al. (2012)
28 shoemakers (18 exposed to benzene at < 10 ppm, 10 at ≥ 10 ppm), 14 clothing factory controls	NR	Low, 2.64 (mean) High, 24.19 (mean) (Based on multiple samples over 3 mo)	+ dr for monosomy 7 and 8; no trisomy effects	Chromosomes 7 and 8; in interphase CFU-GM cells	Zhang et al. (2012a)
722 AML cases, 78 with benzene exposure (10.8%), 38 > 0.31 ppm			– *	–5/5q–, –7/7q–, +8, del(20q) and 11q23/*MLL*; t(8,21), t(15,17) * – for benzene-exposed vs non-exposed AML cases	Irons et al. (2013)

[a] Benzene exposure level conversion: 1 ppm = 3.19 mg/m^3 = 3190 ug/m^3

[b] +, positive; (+), positive but in a study of limited quality; –, negative

AML, acute myeloid leukaemia; CA, chromosomal aberration; CFU-GM, colony-forming-unit granulocyte-macrophage; CWAS, chromosome-wide aneuploidy study; dr, dose–response relationship; FISH, fluorescence in situ hybridization; GM, geometric mean; h, hour(s); HQ, hydroquinone; LOD, limit of detection; MDS, myelodysplastic syndrome; *MLL*, mixed lineage leukaemia gene; mo, month(s); NR, not reported; PBL, peripheral blood lymphocyte; ppm, parts per million; TWA, time-weighted average; vs, versus

–5q, and –7q, as well as for +8 in PBLs, have been observed (Zhang et al., 1998a, 1999, 2011). Zhang et al. (2012a) also observed a significant exposure-related trend for –7, but not +7 or +8, in circulating interphase colony-forming-unit (CFU) granulocyte-macrophage (GM) cells, myeloid progenitor cells that are probable targets for the induction of myeloid leukaemia. In independent studies with PBLs, the benzene-associated aneuploidy of chromosome 7 (Kim et al., 2010) and +8 (Kim et al., 2004b) were confirmed. Zhang et al. (2007) also observed a significant exposure-related trend for trisomy 12.

In studies on several translocations implicated in some cancers of the lymphoid and haematopoietic tissues, Smith et al. (1998) observed a significant exposure-related trend using fluorescence in situ hybridization testing for t(8,21). This association was independently confirmed by Kim et al. (2004b), but not replicated using polymerase chain reaction analysis (McHale et al., 2008; IARC, 2012). Similarly, using fluorescence in situ hybridization Zhang et al. (2007) observed a significant exposure-related increase in t(14,18) in the group exposed to the highest concentration of benzene, but this was not replicated in the polymerase chain reaction analyses of McHale et al. (2008). In addition, Zhang et al. (2007) did not observe significant trends for some common translocations involving the *MLL* (mixed lineage leukaemia) gene on chromosome 11q23; however, a significant exposure-related trend was observed for –6q. McHale et al. (2008) did not observe an exposure-related effect on t(15,17).

In vitro studies similarly report certain cytogenetic changes with exposure to benzene or its metabolites. For example, Chung & Kim (2002) reported significant concentration-related trends for –5 and –7, as well as inductions of +8 without significant trends, in human lymphocytes treated with the benzene metabolites hydroquinone, benzenetriol, or t,t-MA, although no t(8,21) translocations were observed. Similarly, Zhang et al. (1998b) reported significant increases in –5 and –7, as well as in –5q and –7q, in human lymphocytes treated with hydroquinone or benzenetriol. Smith et al. (2000) reported that hydroquinone also induced significant positive dose–response relationships in +8 in CD34+ cells and in –7 in both CD34+ and CD34– cells from human cord blood, CD34+ cells being haematopoietic progenitor cells. Stillman et al. (1997, 1999) observed increased –5 and –7 in a human lymphoblastoid cell line from exposure to hydroquinone, but not to catechol. Stillman et al. (1999) further found that catechol acted synergistically with hydroquinone to induce significant positive dose–response relationships in –5 and –7, as well as –5q, which was not observed for hydroquinone alone. A concentration-related trend for +8 was also observed, although it was reportedly not statistically significant. In addition, Stillman et al. (2000) treated human CD34+CD19– bone marrow cells with hydroquinone and reported significant concentration-related trends for –7 and –5q but not –5 or +8; further, a greater susceptibility to hydroquinone- induced –5q and –7 was seen in the bone marrow cells than in the lymphoblastoid cell line. Zhang et al. (2005) exposed lymphocytes in whole blood to hydroquinone or benzenetriol, and reported that chromosomes 5 and 7 were selectively more susceptible to loss induced by those benzene metabolites than several other chromosomes that were examined; further, chromosome 8 was one of a few chromosomes that were more susceptible to gain. Also of note, similar to the findings of Zhang et al. (2007) in workers exposed to benzene, no increases in translocations involving 11q23 were observed in a lymphoblastoid cell line (TK6) treated with hydroquinone (Ji et al., 2009).

In addition to the investigation of chromosomal end-points in healthy people exposed to benzene, some studies have examined cytogenetic changes in cases of acute myeloid leukaemia (AML) or myelodysplastic syndromes

(MDS) in people who have likely been exposed to benzene. Zhang et al. (2002) reviewed 18 cases of AML attributed to benzene exposure from case reports with cytogenetic analyses. Only 1 of the 18 cases had a normal karyotype (Zhang et al., 2002), in contrast to some cytogenetic studies which reported over 40% of de novo cases of AML with a normal karyotype (Schoch et al., 2004; Sanderson et al., 2006). Zhang et al. (2002) also reviewed over 30 abnormal karyotypes from leukaemia patients with likely prior benzene exposure from several large-scale leukaemia studies, and noted that several cases exhibited the same translocation (e.g. t(8,21) for AML and t(9,22) for chronic myeloid leukaemia). Overall, Zhang et al. (2002) found that there were insufficient data from which to discern a specific pattern of clonal chromosomal changes in patients with leukaemia associated with benzene, indicating that benzene produces a variety of cytogenetic changes that may induce or contribute to leukaemogenesis.

Irons et al. (2013) investigated 722 AML cases identified in Shanghai, China and determined that 78 cases had likely benzene exposure. Irons et al. (2013) compared the cytogenetic findings in the 78 cases exposed to benzene first with those from the 644 unexposed cases and then with those from several studies of therapy-related AML. In a subsequent study of 710 of these AML cases, 75 of which were determined to have likely been exposed to benzene, Kerzic & Irons (2017) assessed chromosome breakpoints across 441 identifiable regions. Likewise, Irons et al. (2010) studied 649 MDS cases in Shanghai, China, and determined that 80 cases had likely been exposed to benzene, 29 of which had likely been exposed to high concentrations (> 21 ppm) of benzene. Irons et al. (2010) first compared the cytogenetic findings in the cases exposed to benzene with those from all of the MDS cases. A case–case analysis was then conducted, in which each of the 29 highly exposed cases was matched by age and sex to two cases with no suspected benzene exposure, and levels of various abnormalities characteristic of t-MDS in the highly exposed cases were compared with levels in the unexposed cases. [The Working Group noted that the implications of the reported comparisons between cases exposed to benzene and unexposed cases are uncertain, given that only a portion of the MDS cases in those exposed to benzene were actually attributable to benzene, which can have a diluting effect.]

(ii) Experimental systems

Benzene induced CAs, MN, and SCEs in bone marrow cells of mice, CAs in bone marrow cells of rats, rabbits, and Chinese hamsters, and sperm-head anomalies in mice treated in vivo. Most of the induced aberrations were breaks or deletions. Chromosome-type aberrations also occurred however, particularly after prolonged exposure when toxicity, manifested by a drop in the peripheral blood leukocyte count, appeared. Benzene did not induce SCE in rodent cells in vitro, but it did induce aneuploidy and CAs in cultured Syrian hamster embryo cells. Benzene induced mutation and DNA damage in some studies in rodent cells in vitro. In *Drosophila*, benzene was reported to be weakly positive in assays for somatic mutation and for crossing-over in spermatogonia; in single studies, it did not induce sex-linked recessive lethal mutations or translocations. It induced aneuploidy, mutation, and gene conversion in fungi. Benzene was not mutagenic to bacteria (IARC, 1982, 1987, 2012). In agreement with a possible role of combinations of multiple metabolites of benzene in genotoxicity, Barale et al. (1990) demonstrated that combinations of phenol and hydroquinone were highly genotoxic to mouse bone marrow as indicated by the formation of MN.

In utero exposure to benzene increased the frequency of MN and SCEs in haematopoietic tissue of fetal and postnatal mice (Ning et al., 1991; Xing et al., 1992). French et al. (2015) observed a dose-dependent increase in benzene-induced

chromosomal damage and estimated a benchmark concentration limit of 0.205 ppm benzene using Diversity Outbred mice. This estimate is an order of magnitude below the value estimated using B6C3F1 mice.

After exposure of mice to benzene, DNA adducts were detected by ^{32}P-postlabelling in both the bone marrow and leukocytes (Bodell et al., 1996; Lévay et al., 1996). Mild but statistically significant mutagenic responses were found in transgenic mice carrying the *lacI* reporter gene exposed to benzene (Mullin et al., 1995; Provost et al., 1996). The clastogenic potential of benzene is partly due to its metabolites. Specifically, benzene oxide, benzoquinones, muconaldehydes, and benzene dihydrodiol epoxides are electrophiles that readily react with peptides, proteins, and DNA (Bechtold et al., 1992b; McDonald et al., 1993; Bodell et al., 1996; Gaskell et al., 2005; Henderson et al., 2005a; Waidyanatha & Rappaport, 2005), and can thereby interfere with cellular function (Smith, 1996).

The importance of CYP2E1 (see Section 4.1) in inducing benzene toxicity was shown in studies of *Cyp2e1*$^{-/-}$ mice, in which no benzene-induced cytotoxicity or genotoxicity were observed (Valentine et al., 1996). Similar studies showed the importance of NQO1, which detoxifies benzoquinones, proposed toxic metabolites of benzene. Compared with *NQO1*$^{+/+}$ mice, *NQO1*$^{-/-}$ mice exhibited more severe benzene-induced haematotoxicity and were more sensitive to benzene-induced MN formation in peripheral blood cells. These results indicate that NQO1 deficiency results in substantially greater benzene-induced toxicity. However, the specific patterns of toxicity differed between the male and female mice (Bauer et al., 2003). In fact, male mice were more sensitive than females to the induction of MN by benzene administered either orally or intraperitoneally (Meyne & Legator, 1980; Siou et al., 1981). This may be due, at least in part, to a function of greater oxidative metabolism in male mice (Kenyon et al., 1996). Castration of males reduces their sensitivity to that of females (Siou et al., 1981).

4.2.3 Altered DNA repair or genomic instability

Several DNA reactive metabolites are formed during benzene metabolism, and the type and the frequency of lesions, the respective DNA repair systems involved in their removal, and the repair capacity of the target organ are influenced by the different metabolites (Winn, 2003; Pandey et al., 2009; Au et al., 2010; Hartwig, 2010). Table 4.7 reports examples of in vivo and in vitro studies indicating altered DNA repair or epigenetic alterations related to benzene exposure or its metabolites.

Benzene exposure at occupational and environmental concentrations influences DNA repair systems in human studies in vivo, as reviewed by Ravegnini et al. (2015). In subjects who worked at a spray-painting plant, the exposure to benzene had significantly altered mRNA expression of some critical cell regulatory and DNA repair genes such as *Xpc*, *Xpa*, and *Apel* (Wang et al., 2012). Exposure to a time-weighted average concentration of benzene in a workplace of up to 1.8 mg/m^3 may cause chromosomal damage in workers; in particular, the *XRCC1* rs25487 and rs1799782 polymorphisms may be associated with an increase in MN frequency (Huang et al., 2016). Frequencies of MN and CAs in 108 petroleum refinery workers exposed to 0.51 ppm of benzene (full-shift time-weighted average) were higher than in 33 office workers, and the frequencies were influenced by the polymorphism of the *XRCC1* gene (Kim et al., 2008).

In human cell systems and in exposed mice, chemically reactive benzene metabolites, particularly 1,4-benzoquinone and hydroquinone, directly inhibited isolated topoisomerase II (Frantz et al., 1996; Hutt & Kalf, 1996; Eastmond et al., 2001, 2005; Ji et al., 2009). Possible mechanisms of this inhibition include covalent binding

Table 4.7 Studies of benzene or metabolites indicating altered DNA repair, genomic instability, or epigenetic alterations

Description of exposed and controls Study type Tissue	Benzene exposure (range or median) or its metabolites	Comments	Reference
DNA repair or genomic instability			
In vitro Isolated topoisomerase IIα	BQ, 10 μM; HQ 10 mM	Metabolites catalytically inhibited topoisomerase II	Baker et al. (2001)
In vitro Isolated topoisomerase IIα; human CEM leukaemia	BQ, 0–100 μM BQ, 10 μM	BQ strongly inhibited topoisomerase II BQ underwent covalent binding with topoisomerase IIα	Lindsey et al. (2004)
108 exposed petroleum refinery workers, 33 controls Occupational exposure	0.004–4.52 ppm	Both the CA and MN frequencies were significantly higher in exposed compared with unexposed workers and influenced by polymorphism of XCCR1 gene	Kim et al. (2008)
Spray painters: A, 46 direct exposed; B, 26 indirect exposed; C, 29 controls Occupational exposure	A, 0.21 ± 0.19 mg/m^3; B, 0.06 ± 0.12 mg/m^3; C, ND	The mRNA expression levels of *Rad51*, *Bcl-2*, *Bax*, *Apel*, *Xpa*, and *Xpc* in groups A and B were downregulated significantly compared with group C	Wang et al. (2012)
Haematopoietic stem and progenitor cells, human CD34+ cells In vitro	0.5–1 mg/mL	DNA breakage	Thys et al. (2015)
CD-1 mouse fetal liver cells In vitro	BQ, 5, 15, and 25 μM	Benzoquinone exposure significantly decreased the transcript levels of 8-oxo-guanine glycosylase	Philbrook & Winn (2016)
Epigenetic alterations			
DNA methylation			
78 gas station attendants, 77 urban traffic officers, and 57 controls Occupational exposure	0.040–0.132, 0.09–0.031, and < 0.006–0.014 mg/m^3	Airborne benzene was associated with hypomethylation of *Line-1* and *AluI*	Bollati et al. (2007)
In vitro Human lymphoblastoid TK6 cells	Benzene: 1, 10, and 100 μM; HQ, 0.005, 0.05, and 0.5 μM	Benzene and its metabolite HQ exposure induced global DNA hypomethylation in TK6 cells	Tabish et al. (2012)
In vitro Human hepatic L02 cells	Benzene, HQ, and BQ: 5, 10, 25, and 50 μM	HQ and 1,4-BQ, but not benzene, induced global DNA hypomethylation	Hu et al. (2014)
Histone modifications			
In vitro Human myeloid leukaemia HL-60 cells	HQ Single treatment: 1, 5, 15, and 25 μM Repeated treatment: 1, 5, and 15 μM four times every 48 h Long-term treatment with 1μM: five times a week for 5 wk	Epigenetic modifications (instauration in *LINE-1* sequences) after in vitro treatment with HQ were transitory and reversible	Mancini et al. (2017)

BQ, benzoquinone; CA, chromosomal aberration; CEM, human acute lymphoblastic leukaemia cells; h, hour(s); HQ, hydroquinone; *LINE-1*, long interspersed nuclear element-1; MN, micronuclei; ND, not detectable; ppm, parts per million; wk, week(s)

or catalytic action (Baker et al., 2001; Lindsey et al., 2004, 2005; Chen et al., 2016a).

Benzoquinone exposure significantly decreased the transcript levels of the critical base excision repair gene, 8-oxo-guanine glycosylase, in CD-1 mouse fetal liver cells in vitro (Philbrook & Winn, 2016); it was also able to rapidly increase ROS production, followed by a statistically significant increase in both c-H2A.X foci and DNA recombination in fetal haematopoietic cells (Tung et al., 2012).

4.2.4 Immunosuppression

This section focuses on the studies that directly or indirectly inform immune response outcomes, and is divided into haematotoxicity (inclusive of all such data in Section 4), genes related to immune function, and immunoproteins.

(a) Humans

(i) Haematotoxicity

Acute exposure to benzene has been associated with diseases and symptoms in the blood-forming system such as aplastic anaemia, specific cytopenias, and pancytopenia (Aksoy et al., 1971; Yin et al., 1987; IARC, 2012). These diseases are associated with a functional reduction in immune competence by virtue of the reduced number of immunocompetent cells resulting from impaired haematopoiesis (IARC, 2012; McHale et al., 2012). In addition, several studies have found that various levels of severity of benzene-associated haematotoxicity have been associated with a future risk of developing a haematological malignancy or related disorder (Aksoy & Erdem, 1978; Yin et al., 1987; Rothman et al., 1997).

Many studies investigating the association between benzene exposure and altered blood cell counts reported haematological changes in exposed humans, especially at relatively high levels of exposure (e.g. > 10 ppm) (Rothman et al., 1996; Ward et al., 1996; Qu et al., 2002; Lan et al., 2004); some studies have demonstrated that haematological alterations can also occur at lower levels of exposure (< 10 ppm) (Ward et al., 1996; Zhang, 1996; Qu et al., 2002; Lan et al., 2004; Miao & Fu, 2004; Uzma et al., 2008; Robert Schnatter et al., 2010; Chen et al., 2012; Wang et al., 2012; Zhang et al., 2016). In particular, leukocyte counts were consistently reduced in an exposure-related manner (Rothman et al., 1996; Ward et al., 1996; Qu et al., 2002; Lan et al., 2004; Robert Schnatter et al., 2010). Reductions in leukocyte counts were observed with median benzene air concentrations of 1.2 ppm in Lan et al. (2004) and 3.8 ppm (4-week average) in Qu et al. (2002), with lowered counts in subgroups of workers exposed to less than 1 ppm. Decreased neutrophil counts were associated with benzene exposure down to a level of about 7.8–8.2 ppm (Robert Schnatter et al., 2010). However, numbers of band neutrophils, which are precursors and later mature into granulocytes, were increased as well as mean corpuscular volume (Bogadi-Sare et al., 2003).

A few studies reported no statistically significant differences in blood cell counts (Hancock et al., 1984; Kipen et al., 1989; Biró et al., 2002). Additionally, several studies reported no or minimal changes in haematological parameters in workers with occupational exposures of less than 5 ppm, in particular, less than 1 ppm. Several of these studies used historical haematological data collected as part of routine surveillance (Collins et al., 1991, 1997; Tsai et al., 2004; Swaen et al., 2010). [The Working Group noted that the timing of collection of blood samples relative to the most recent benzene exposure was not reported.]

Total lymphocyte counts were reduced in humans exposed to benzene (Rothman et al., 1996). Numbers of circulating CD19+ B-lymphocytes were consistently reduced in several studies (Rothman et al., 1996; Bogadi-Sare et al., 2000, 2003; Lan et al., 2004). CD4+ T-lymphocytes were consistently decreased in

multiple studies (Luan, 1992; Lan et al., 2004; Kirkeleit et al., 2006; Uzma et al., 2008; Chen et al., 2007, 2012; Wang et al., 2012); however, CD8+ T-lymphocyte populations were increased (Chen et al., 2012). In a study of paint factory workers exposed to benzene, a continual increase in the percentage of CD8+ T-cells measured every 4 months for a year was observed (Chen et al., 2012). No significant change in absolute number of CD8+ cells was observed in other studies (e.g., Chen et al., 2007). The decreased CD4+ and increased CD8+ T-cells resulted in a lowering of the CD4+/CD8+ ratio (Luan, 1992; Lan et al., 2004; Chen et al., 2007, 2012; Wang et al., 2012). Increased CD3+ lymphocytes were additionally noted (Chen et al., 2012).

Benzene exposure also reduced T-cell receptor excision circles (TRECs), a marker of T-cell maturity. Decreased TRECs in peripheral blood mononuclear cells (PBMCs) of patients with benzene poisoning were found in two separate studies, suggesting impaired T-cell immune function (Li et al., 2005, 2009a). Decreased TRECs were also found in the peripheral blood mononuclear cells in 62 workers exposed to benzene at a concentration in air of 1.72–37.8 mg/m^3 compared with 11 healthy controls (Han et al., 2004). However, Lan et al. (2005a) reported no significant difference in TREC levels in shoe factory workers exposed to benzene at a mean concentration in air of 15.8 ppm.

Relatively low levels of benzene (i.e. < 5 ppm) could result in haematological suppression after continuous exposure with no observed threshold for a response (Ward et al., 1996). Most types of blood cells, with the exception of leukocytes, from complete blood count levels were decreased in workers exposed to benzene, correlated with length of employment (Khuder et al., 1999).

Overall, decreased red blood cell counts (Rothman et al., 1996; Khuder et al., 1999; Qu et al., 2002; Miao & Fu, 2004; Koh et al., 2015), platelets (Rothman et al., 1996; Qu et al., 2002; Uzma et al., 2008; Ye et al., 2008; Chen et al., 2012; Wang et al., 2012), and haemoglobin content (Bogadi-Sare et al., 2003; Wang et al., 2012; D'Andrea & Reddy, 2016) were consistently reported. Benzene exposure increased haemoglobulin content and platelets. Haemoglobin content and red blood cell counts in workers who had been exposed to benzene for longer periods were significantly increased compared with controls (Uzma et al., 2008). Chemical and rubber factory workers who had been exposed to benzene at 0.07–872.0 mg/m^3 (median level, 7.4 mg/m^3) had reduced red blood cell count and mean platelet volume, the most affected haematological peripheral blood parameters (Robert Schnatter et al., 2010).

Finally, several studies examined circulating haematopoietic stem and/or progenitor cells, which may also be affected in individuals exposed to benzene. In a cross-sectional study of 17 petroleum refinery workers exposed to very low levels of benzene (0.28–0.41 ppm), increased burst-forming-unit erythroid and CFU-GM colonies without any growth stimulation were observed compared with 20 unexposed controls; this effect was not observed after the addition of growth factors, either erythropoietin (EPO) or granulocyte colony-stimulating factor (Quitt et al., 2004). However, another study of 10 subjects with occupational exposure to more than 10 ppm benzene (mean, 24.2 ppm), 19 subjects with exposure to less than 10 ppm benzene (mean, 2.6 ppm), and 24 controls with no occupational exposure to benzene reported an inverse monotonic exposure–response relationship with haematopoietic progenitor cell colony formation in cultured peripheral blood, including: CFU granulocyte, erythroid, macrophage, and megakaryocyte (with EPO stimulation); CFU-GM (with and without EPO stimulation); and burst-forming-unit erythroid cells (with EPO stimulation) (Lan et al., 2004).

(ii) Genes related to immune function

Several studies have investigated human susceptibility to benzene exposure and its relationship with single-nucleotide polymorphisms in genes that encode immune-related proteins. For instance, the tumor necrosis factor alpha (TNF-α) single-nucleotide polymorphism was associated specifically with an increased risk of persistent benzene-induced dysplasia in workers (Lv et al., 2007), and a significantly higher frequency of TNF-α was observed in benzene-poisoned patients (Lv et al., 2005).

Corresponding to altered leukocyte counts in benzene-exposed shoe factory workers, changes were reported in the expression of various genes, including the vascular cell adhesion molecule *VCAM1*, interleukin (*IL*)*-1A*, *IL-4*, *IL-10*, *IL-12A*, *CSF3*, *MPO*, and *CRP* (Lan et al., 2005b; Shen et al., 2011). Gene expression related to T-cells was also altered. The distributions of the T-cell receptor variable (TCRV) family TCRVα, TCRV*β*, and TCRVγ gene repertoires in individuals exposed to benzene were significantly lower compared with the reference group (Chen et al., 2006; Li et al., 2007, 2008, 2009b). PBMC gene expression levels of *CD3δ*, *CD3ε*, and *CD3ζ* were increased in workers exposed to benzene versus controls; in workers diagnosed with benzene poisoning, however, some regions were decreased in severe cases and other regions were unchanged (i.e. *CD3γ* and *CD3ε*) in mild cases (Li et al., 2012). *CXCL16*, a gene responsible for encoding a chemokine that activates T-cells and natural killer cells, was found to be consistently upregulated in workers exposed to benzene (Forrest et al., 2005; McHale et al., 2009).

(iii) Immunoproteins

Regarding B-cell effects, immunoglobulin (Ig) G production was positively correlated with air benzene levels (Bogadi-Sare et al., 2000). Increased IgG was also reportedly correlated with benzene urinary metabolite t,t-MA measured in petrochemical workers exposed to benzene (Dimitrova et al., 2005). IgM and IgA were reduced in cargo tank workers exposed to benzene (Kirkeleit et al., 2006). Furthermore, one study reported that plasma concentrations of soluble CD27 and CD30, two immune markers indicative of B-cell activation, were decreased by 17% for sCD27 but non-significantly reduced for sCD30 in the group exposed to the highest concentration of benzene (≥ 10 ppm) compared with control workers, after adjusting for age and sex (Bassig et al., 2016). [The Working Group noted that several prospective cohorts, although not specifically related to benzene, found that higher levels of sCD27 were associated with increased risk of non-Hodgkin lymphoma (Purdue et al., 2011; De Roos et al., 2012; Bassig et al., 2015a; Hosnijeh et al., 2016; Späth et al., 2017).]

Similar to effects in cytokine gene expression, cytokine serum concentrations were also modified. TNF production was significantly reduced in paint factory workers exposed to benzene vapours (Haro-García et al., 2012). IL-10 serum concentrations were positively correlated with the number of working years in those exposed to benzene (Spatari et al., 2015).

(b) Human cells in vitro

Alterations in cytokine production were also observed in studies of human cells in vitro. Both IL-1α and IL-1β were decreased in human blood monocytes after exposure to hydroquinone (Carbonnelle et al., 1995). Catechol, hydroquinone, 1,2,4-benzenetriol, and *p*-benzoquinone were also found to stimulate the production of T-helper cell (Th2) cytokines IL-4 and IL-5 (Gillis et al., 2007).

Supporting the haematotoxicity observed in humans, phenol, hydroquinone, and 1,2,4-benzenetriol decreased haemoglobin synthesis in K562 cells in a concentration-dependent manner (Wu et al., 2011). CD34+ haematopoietic progenitor cells treated with hydroquinone inhibited erythroid differentiation

in an exposure-related response, and miRNA-451a and miRNA-486–5p were upregulated during erythroid differentiation (Liang et al., 2017).

(c) Experimental systems

(i) Mouse

Several murine studies demonstrated consistent immunosuppressive effects on assays for humoral and cell-mediated immune function after oral and inhalation exposure. The only animal study to evaluate the effect of benzene exposure on the ability of T-cells to respond to a tumour challenge was conducted by Rosenthal & Snyder (1987), who exposed C57Bl/6 male mice to three concentrations (10, 30, and 100 ppm) of benzene for 100 days before tumour challenge. Inhalational exposure to 100 ppm increased lethal tumour incidence, which suggests reduced tumour surveillance (Rosenthal & Snyder, 1987). Further examination demonstrated that the same benzene concentration reduced T-cell cytolytic activity after 20 days of exposure, and reduced proliferative responses in the spleen in the mixed lymphocyte reaction (Rosenthal & Snyder, 1987). These reductions in cytotoxic and proliferative activity all occurred without any corresponding changes in the total number of T-cell or lymphocyte subpopulations in the spleen (Rosenthal & Snyder, 1987). In addition, Rosenthal & Snyder (1985) also demonstrated that 9 days of continuous inhalation exposure to benzene reduced cell-mediated immunity to bacterial infection. Exposure to benzene at several concentrations (30–300 ppm) increased bacterial load after a 4-day infection by the intracellular pathogen *Listeria monocytogenes*. Accompanying this effect, total lymphocytes and T- and B-cell populations were all reduced in the spleen for up to 7 days post-infection under the same benzene exposure concentrations (Rosenthal & Snyder, 1985).

Changes in assays for humoral immune function were first observed in BALB/c male mice after inhalation exposure to benzene at concentrations of 50 or 200 ppm for 14 days (Aoyama, 1986). Seven days after immunization with sheep red blood cells (SRBC), both benzene concentrations reduced IgM SRBC-specific plaque-forming cells (PFC) by up to 87% relative to controls, and IgG PFCs were reduced by approximately 94% (Aoyama, 1986). IgG PFCs remained suppressed 10 days after immunization, and IgM PFCs were not significantly different from controls. Reductions in total lymphocytes and B- and T-cells in the blood were also observed at the same concentration.

The oral exposure database of assays for immune function is less robust than that for inhalation; only one study has reported reduced humoral immunity. Male CD-1 mice were exposed to benzene in drinking-water at a concentration of 166 mg/L (the only tested dose) for 28 days, resulting in reduced IgM SRBC-specific PFCs as well as anti-SRBC antibody titres (Hsieh et al., 1990). Reductions were also observed in the mixed lymphocyte response and T-cell proliferation in response to concanavalin A and phytohaemagglutinin stimulation, and in the B-cell proliferative responses to pokeweed mitogen and lipopolysaccharide stimulation. In addition, benzene exposure increased serum corticosterone, which is known to suppress immune function (Hsieh et al., 1991). Different results were observed in a study of BALB/c male mice exposed to benzene by oral gavage at a concentration of 150 mg/kg bw per day (8 hours per day/5 days a week, for 2 weeks); no changes in total serum antibody titres were reported, but reduced counts of leukocytes, total lymphocytes, monocytes, and neutrophils in the blood were observed (Wen et al., 2016). In C57BL/6 mice exposed orally to benzene at 27 mg/kg bw per day for 28 days, briefly increased splenic natural killer cell activity was observed by day 21 and

splenic production of IL-2 was reduced by day 28 (Fan, 1992).

The haematotoxic effects of benzene exposure are well established in experimental animals (Cronkite et al., 1985; Farris et al., 1997a). Rats and mice of both sexes exhibited leukocytopenia and anaemia after subchronic inhalation exposure, but only mice demonstrated evidence of severe femoral hypoplasia (Ward et al., 1985). Nucleated bone marrow cells were significantly reduced in $B6C3F_1$ mice after inhalation exposure at a concentration of 100 ppm benzene for 8 weeks (Farris et al., 1997a). From analysis of the differentiation and maturation of haematopoietic precursor cells, exposure to benzene at 200 ppm for 8 weeks resulted in a sustained reduction of the primitive precursor CFU high proliferative progenitor cells, downstream progenitor CFU-GM cells, bone marrow granulocytes, and leukocytes in the blood (Farris et al., 1997a). In C57BL/6 mice exposed intraperitoneally to hydroquinone at 50 mg/kg bw per day or to benzene at 600 mg/kg bw per day for 2 days, or in DBA/2J mice exposed to benzene at 10 ppm via inhalation for 5 days, CFU-GM proliferation was not significantly affected but differentiation was significantly increased (Dempster & Snyder, 1991; Hazel et al., 1996). When Swiss Webster mice of both sexes were exposed to benzene in utero at 10 ppm and re-exposed to benzene at 10 ppm at age 10 weeks, greater reductions in splenic CFU-GM were observed compared with mice that were not exposed to benzene in utero (Keller & Snyder, 1986). Intraperitoneal exposure to benzene increased the production of nitric oxide in bone marrow cells, which may contribute to the reduced proliferation (Punjabi et al., 1994). Benzene exposure was also found to suppress the progenitor cell cycle of CFU-GM in the bone marrow of C57BL/6 mice by overexpressing the cyclin-dependent kinase inhibitor p21 (Yoon et al., 2001).

(ii) Rat

Two rat studies examined the effect of benzene exposure on assays for immune function: one oral and one inhalation. In male Wistar rats exposed to a single dose of benzene in drinking-water at 0.6 mL/kg of drinking water per day for 90 days, reductions in the total number of SRBC-specific antibody-forming cells in the spleen by 40%, and in the total anti-SRBC serum titres by 64% after immunization with SRBC (immunization protocol not specified), were observed (Karaulov et al., 2017). Cell-mediated immunity, assessed by the delayed-type hypersensitivity response, was also reduced by 52% compared with controls. Karaulov et al. (2017) additionally examined the effect of benzene exposure after 45, 90, and 135 days by stimulating splenocytes ex vivo with the concanavalin A; increased cytokine production of IL-4 and IL-6 and a reduced number of CD4+ T-cells were reported for all time periods.

In male Sprague-Dawley rats exposed to benzene via inhalation at a range of concentrations (30–400 ppm) for 2 or 4 weeks, no changes in anti-SRBC serum antibodies were induced (Robinson et al., 1997). However, the highest tested concentration reduced the numbers of splenic B-cells after 2 and 4 weeks of exposure and of CD4+/CD5+ T-helper cells after 4 weeks of exposure.

4.2.5 Altered cell proliferation, cell death, and nutrient supply

(a) Humans

Representative studies were included if the biological end-point was considered relevant for this key characteristic (studies of peripheral blood cell counts, benzene poisoning, cultured haematological progenitor cells, and genetic susceptibility to these events are presented in Section 4.2.4(a)). The Working Group focused on studies in which presence of benzene in the study population was documented, the presence

of co-exposures was evaluated and addressed, the control group was comparable to the exposed study population, and the study had adequate statistical power.

A case series report in China of 23 subjects with a history of benzene poisoning, with quantitative data for 17 subjects indicating very high exposure to benzene before diagnosis (i.e. concentration in air at 50–300 ppm), described a distinct pattern of bone marrow dysplasia including marked dyserythropoiesis, eosinophilic dysplasia, and abnormal cytoplasmic granulation of neutrophilic precursors. In addition, clonal and oligoclonal proliferation in bone marrow T-lymphocytes, including clonal rearrangements in T-cell receptor gene segments, was present in 14 out of 23 cases (Irons et al., 2005).

Several cross-sectional studies of workers with occupational exposure to benzene and unexposed controls measured miRNA in peripheral leukocytes or plasma and mRNA in leukocytes, and found altered levels of these end-points for genes that play a role in apoptosis; these studies provided indirect evidence of the possible influence of benzene on apoptosis in healthy subjects (Forrest et al., 2005; Sun et al., 2009; McHale et al., 2011; Wang et al., 2012; Li et al., 2014; Chen et al., 2016b, 2017; Hu et al., 2016; Liu et al., 2016).

In studies in vitro, benzene or its metabolites induced apoptosis in CD34+ human bone marrow progenitor cells, PBLs, PBMCs, bone marrow mesenchymal stem cells, and HL-60 human promyelocytic leukaemia cells (Moran et al., 1996; Ross et al., 1996a; Wiemels & Smith, 1999; Bratton et al., 2000; Nishikawa et al., 2011; Hu et al., 2012; Lee et al., 2012; Peng et al., 2012; Zolghadr et al., 2012). Inhibition of nuclear-factor kappa-light-chain-enhancer of activated B-cells (NF-κB) by hydroquinone sensitizes human bone marrow progenitor cells to TNF-α-induced apoptosis (Kerzic et al., 2003). Inhibition of DNA-dependent protein kinase, catalytic subunit, potentiated the apoptotic and growth inhibitory effects of hydroquinone in proerythroid leukaemia K562 cells (You et al., 2013). Apoptosis was prevented when NQO1 was induced by hydroquinone in KG-1a human promyeloblastic leukaemia cells. Induction of NQO1 by hydroquinone in human bone marrow cells depends on its genotype (Moran et al., 1999); in cells with a T/T genotype, NQO1 activity and protein were not detected (Ross et al., 1996b; Traver et al., 1997). This finding is consistent with the observation that the NQO1 null genotype increases the risk of benzene poisoning (i.e. haematotoxicity) (Rothman et al., 1997).

The benzene metabolite orthoquinone stimulated hyperproliferation of human mononuclear cells cultured with T- and B-cell mitogens (Chakravarti et al., 2006).

(b) Experimental systems

Benzene is reported as a bone marrow depressant as it decreases cell counts in circulating blood, bone marrow, and haematopoietic progenitor cells of animals treated with benzene (IARC, 1982). The cycling fraction of bone marrow or progenitor cells is also suppressed during exposure to benzene, although this suppression is rapidly reversed when exposure to benzene ceases (Moeschlin & Speck, 1967; Irons et al., 1979; Cronkite et al., 1982; Lee & Garner, 1991; Farris et al., 1997a). Suppression of the number of progenitor cells as well as of their cycling fraction is induced by a p53-mediated checkpoint for damaged cells (Kastan et al., 1991; el-Deiry et al., 1994), as evidenced by the lack of suppression of either parameter in the Trp53 knockout mouse (Yoon et al., 2001). On and off regulation of Trp53 therefore results not only in the direct suppression of haemopoiesis but also in a dynamic recovery proliferation after suppression of haemopoiesis during and after benzene exposure in wildtype mice. These dynamic changes may be responsible for the oscillatory proliferation of bone marrow cells to counter any additional epigenetic haematopoietic

neoplastic impacts (Yoon et al., 2001). Indeed, the studies of Snyder and co-workers (Snyder et al., 1981; Dempster & Snyder, 1990) demonstrated that exposing mice to benzene by inhalation for varying periods of time resulted in a growth advantage for granulopoietic cells and proliferation of myeloblasts and/or promyelocytes.

Benzene has been shown to induce apoptosis in murine haematopoietic cells in vitro (Martínez-Velázquez et al., 2006; Gao et al., 2011), as well as spleen cells, femoral B-lymphocytes, and thymic T-lymphocytes in vivo (Farris et al., 1997b; Wen et al., 2016). In mice exposed to benzene by inhalation at 100 ppm for 6 hours per day, 5 days per week for 2 weeks, no change in the level of apoptosis in bone marrow as measured by flow cytometric analysis using Annexin V staining (Faiola et al., 2004) was observed. However, genes involved in apoptosis (Trp53-mediated *caspase 11*, *bax*, and *ccng*) were upregulated in the bone marrow cells of mice exposed to benzene by inhalation at 300 ppm for 6 hours per day, 5 days per week for 2 weeks (Yoon et al., 2003). In mice exposed to benzene by inhalation at 300 ppm for 6 hours per day, 5 days per week, a higher ratio of apoptosis (i.e. Annexin V staining) in bone marrow cells was observed on day 60 after the start of the experiment when compared with control mice (Das et al., 2012). Trp53-mediated gene expression alterations were also observed in the bone marrow cells of mice exposed to benzene by inhalation at 100 ppm for 6 hours per day, 5 days per week for 15 weeks (Boley et al., 2002). Simultaneously, in mice exposed to benzene a reduction of immune function (phagocytic capacity and cytotoxic efficacy) of cells derived from bone marrow, a reduced generation of adherent stromal cells, and a decreased expression of the adhesion molecule (CXCR4) in bone marrow cells were observed, which might be responsible for inducing myelodysplasia (Das et al., 2012).

Inhalation of benzene at 300 ppm for 23 hours per day for 7 consecutive days induced apoptotic changes in the parenchymal components of the lung of Sprague-Dawley rats. An assay for terminal deoxynucleotidyl transferase dUTP nick end-labelling (TUNEL) and electrophoretic analysis of internucleosomal DNA fragmentation of benzene-exposed lung tissue exhibited 180–200 base pairs of laddering subunits, indicative of genomic DNA degradation (Weaver et al., 2007).

4.2.6 Receptor-mediated effects

Although no data on aryl hydrocarbon receptor (AhR) were available in exposed humans or in human cells, several experimental studies in vitro and in vivo have examined the potential role of AhR in benzene carcinogenicity. This transcription factor appears to be involved in the regulation of immature haematopoietic stem or progenitor cell populations, and AhR dysregulation may result in changes to the bone marrow microenvironment that can lead to excessive or unnecessary proliferation (Singh et al., 2009, 2014). Yoon et al. (2002) reported that AhR-knockout ($AhR^{-/-}$) mice do not show any haematotoxicity after exposure to benzene (Yoon et al., 2002). Follow-up studies reported that mice in which the bone was ablated by irradiation and repopulated with marrow cells from AhR-knockout mice did not display any sign of benzene-induced haematotoxicity (Hirabayashi et al., 2008; Hirabayashi & Inoue, 2010). Benzene and its metabolites hydroquinone and benzoquinone did not activate AhR in mouse hepatoma cells in vitro, suggesting that direct interaction with AhR is not involved in these haematotoxic effects (Badham & Winn, 2007).

4.2.7 Chronic inflammation

(a) Humans

TNF-α (an important mediator of inflammation), IL-6 (a pro-inflammatory cytokine), and IL-8 (a chemokine) were studied in 196

rural Indian women who used benzene-contaminated biomass to cook, and compared with 149 age-matched women who cooked with the cleaner fuel of liquefied petroleum gas (Dutta et al., 2013). This study analysed sputum samples and revealed markedly elevated levels of TNF-α (6.9-fold) as well as significantly higher IL-6 and IL-8 levels in the exposed women, suggesting airway inflammation and trafficking of inflammatory cells from circulation to the airways, compared with control women who cooked with the cleaner fuel (Dutta et al., 2013). [The Working Group noted that the women using biomass were not only exposed to benzene, but also to particulate matter of diameter less than 10 μm (PM_{10}) and other toxic chemicals such as formaldehyde, which may also induce inflammation.]

Several studies in human cells in vitro indicate that several benzene metabolites (t,t-MA, hydroquinone, catechol, benzoquinone, and 1,2,4-benzenetriol) may play important roles in the mechanisms of benzene toxicity and inflammation. Hydroquinone (1–10 M) inhibited TNF-α-induced activation of NF-κB in primary human CD4+ T-lymphocytes and in primary human CD19+ B-lymphocytes (Pyatt et al., 1998, 2000). Gillis et al. (2007) showed that benzene metabolites (catechol, hydroquinone, 1,2,4-benzenetriol, and benzoquinone) increased production of pro-inflammatory cytokines (TNF-α and IL-6) in PBMCs. TNF-α production was increased in a dose-dependent manner. Concurrently, suppression of anti-inflammatory cytokine IL-10 expression was also observed in the activated PBMCs treated with higher concentrations of hydroquinone and catechol (Gillis et al., 2007).

(b) Experimental systems

(i) Mouse

Exposure to benzene for 14 days has been demonstrated to affect inflammation in mouse models in two studies. Aoyama (1986) reported that exposure to benzene by inhalation at 200 ppm for 14 days increased ear swelling in BALB/c mice immunized with the contact sensitizer picryl chloride. In mice given benzene by oral gavage at 150 mg/kg bw per day (8 hours per day/5 days a week, for 2 weeks), slight, but not significant, paw swelling was observed in the delayed-type hypersensitivity test (Wen et al., 2016).

Benzene metabolites were also shown to directly induce inflammatory responses in mice. In C57BL/6 female mice given a single subcutaneous injection (100 nmol/mouse), benzoquinone and (to a lesser extent) hydroquinone, but not benzene itself, was observed to increase popliteal lymph node cell count indices 6 days later as determined by popliteal lymph-node assay (Ewens et al., 1999). Bando et al. (2017) also demonstrated the direct inflammatory capacity of hydroquinone. The ears of BALB/c and C57BL/6 mice were observed to swell within 24 hours of dermal application of hydroquinone at concentrations of as low as 1% and 8%, respectively. Further examination revealed accumulation of Th2 cytokines such as IL-4, decreased Th1 cytokines, and increased accumulation of T-, B-, and natural killer cells, total serum IgE, hydroquinone-specific IgE, macrophages, neutrophils, and eosinophils (Bando et al., 2017). In female BALB/c mice, hydroquinone induced IL-4 and IgE and increased total and keyhole limpet haemocyanin-specific IgE (Lee et al., 2002).

(ii) Rat

In a single rat study that examined the effect of 1 hour of dermal exposure to benzene of hairless male rats, occlusive and unocclusive dermal exposure increased erythema at the site of application. Blood IL-1 and skin concentrations of TNF-α increased by 2.4-fold and 3.7-fold, respectively (Chatterjee et al., 2005).

4.2.8 Epigenetic alterations

Epigenetic alterations related to benzene exposure were observed in studies in vivo and in vitro, as reviewed by Zhang et al. (2010), Chappell et al. (2016), and Salemi et al. (2017).

Epigenetic alterations, including DNA methylation and non-coding RNA, were correlated with benzene exposure (Fenga et al., 2016). Occupational or environmental exposure to benzene can produce epigenomic changes. More recently, the effect of benzene exposure on miRNA expression has been reported in occupationally exposed workers (Liu et al., 2016). Downregulation of miR-133a was observed in 50 workers exposed to benzene at 3.50 ± 1.6 mg/m^3 compared with 50 controls exposed to benzene at 0.06 ± 0.01 mg/m^3 (Chen et al., 2016b). Overexpression of miR-221 was observed in PBLs of 97 petrol station attendants exposed to benzene at 0.073 ± 0.02 mg/m^3 compared with 103 controls exposed to benzene at 0.008 ± 0.001 mg/m^3 (Hu et al., 2016).

The results of in vitro studies of benzene-induced changes in DNA methylation are influenced by cell line type and substance used for the specific experiment, that is, benzene or its metabolite. A global DNA hypomethylation was observed in human lymphoblastoid TK6 cells after exposure to benzene at concentrations of 1, 10, and 100 μM (Tabish et al., 2012), and after exposure to hydroquinone at concentrations of 2.5, 5, 10, 15, and 20 μM in a dose-dependent manner (Ji et al., 2010). In human normal hepatic L02 cells a global DNA methylation change was observed only after exposure to hydroquinone and 1,4-benzoquinone, but not to benzene itself or other metabolites (Hu et al., 2014). A reversible poised state of chromatin, identified by the simultaneous presence of histone modifications associated with both gene activation and repression in long interspersed nuclear element-1 (*LINE-1*) sequences, was observed after an in vitro long-term treatment of human myeloid leukaemia HL-60 cell line with a low-concentration dose (1μM (correspond to 110 ng/mL)) of hydroquinone (Mancini et al., 2017). In human leukaemia U937 cells exposed to 1,4-benzoquinone, Chen et al. (2016b) observed dose-dependent alterations in miR-133a expression.

4.2.9 Other mechanisms

Other effects of benzene primarily concern telomere length and transformation. Bassig et al. (2014) reported that workers who had been exposed to high concentrations of benzene (> 31 ppm) had a mean telomere length that was increased by about 10% compared with matched unexposed workers. A study of human lung cells in vitro reported that exposure to benzene (0.01 and 1 μM) increased telomerase activity in the fibroblast-like human lung LL24 cell line, but not in the human adenocarcinoma A549 cell line at higher concentrations (10 and 1000 μM) (Giuliano et al., 2009).

Two studies in vitro examined indicators of transformation. Tsutsui et al. (1997) reported increases in transformed colonies of Syrian hamster embryo cells after treatment with benzene and its metabolites phenol, catechol, or hydroquinone (1–100 μM), and Ibuki & Goto (2004) described anchorage-independent growth in soft agar after treatment of NIH3T3 cells with benzoquinone and hydroquinone.

4.3 Data relevant to comparisons across agents and end-points

This section analyses the responses and/or activity of benzene, its metabolites (Fig. 4.1), and its agents, as evaluated by IARC in a diverse set of in vitro assays performed as part of the United States Environmental Protection Agency Toxicity Forecaster (ToxCast) (Kavlock et al., 2012) and Toxicology in the 21st Century (Tox21) (Tice et al., 2013) initiatives. The inclusion of analyses from high-throughput in vitro assays in the

evaluation of the carcinogenicity of agents has been identified as a priority by IARC (Straif et al., 2014). Consequently, analyses involving these assays have been part of recent *Monographs* that have evaluated the carcinogenicity of 2,4-dichlorophenoxyacetic acid (2,4-D) and 4,4′-dichlorodiphenyltrichloroethane (DDT) (Loomis et al., 2015).

Benzene has not been tested as part of ToxCast and Tox21. The benzene metabolites that have been evaluated are phenol (IARC Group 3), hydroquinone (IARC Group 3), catechol (IARC Group 2B), and 1,4-benzoquinone (IARC Group 3).

Exposure to agents could potentially lead to human cancer through a diverse set of mechanisms. Each individual agent has a specific pathway or a set of pathways leading to a particular kind of cancer. Despite this heterogeneity in the possible mechanisms, Smith et al. (2016) have identified 10 common characteristics of carcinogens by examining all agents classified as Group 1 carcinogens by IARC. The *IARC Monographs* Volume 113 Working Group (Loomis et al., 2015; IARC, 2017) systemically evaluated the assays performed as part of ToxCast and Tox21 and assigned an estimation of activity in each assay for an agent as an indication of 1 of the 10 key characteristics of the carcinogens. In this *Monograph*, we use these same assignments of activities (i.e. mapping of assays) to the key characteristics. Assays were assigned to 6 out of the 10 key characteristics of carcinogens, namely: is electrophilic or can undergo metabolic activation (31 end-points); induces epigenetic alterations (11 end-points); induces oxidative stress (18 end-points); induces chronic inflammation (45 end-points); modulates receptor-mediated effects (92 end-points); and alters cell proliferation, cell death, or nutrient supply (68 end-points).

The 10 key characteristics are listed in full as follows.

(1) *Is electrophilic or can be metabolically activated*: 31 assay end-points consisting of CYP biochemical activity assays and aromatase, which regulates conversion of androgens to estrogens. [The Working Group noted that these assays largely indicate inhibition of CYP activity, and do not directly measure metabolic activation or electrophilicity.]

(2) *Is genotoxic*: 0 assay end-points.

(3) Alters DNA repair or causes genomic instability: 0 assay end-points.

(4) *Induces epigenetic alterations*: 11 assay end-points including 4 DNA-binding assays in HepG2 liver cell lines, biochemical assays targeting histone deacetylases, and other enzymes modifying chromatin, as well as cellular transcription factor assays involved in epigenetic regulation. [The Working Group noted these end-points have not been extensively validated with reference compounds for epigenetic alterations.]

(5) *Induces oxidative stress*: 18 assay end-points, all cellular assays, targeting nuclear erythroid-related factor-2, antioxidant response element, and other stress-related transcription factors, as well as protein upregulation in response to ROS.

(6) *Induces chronic inflammation*: 45 assay end-points, mostly using primary human cells, measuring protein expression levels indicative of inflammatory responses, including cytokines, cell adhesion molecules, and NF-κB. [The Working Group noted these in vitro end-points are short-term assays and therefore not directly indicative of chronic inflammation.]

(7) *Is immunosuppressive*: 0 assay end-points.

(8) *Modulates receptor-mediated effects*: 92 assay end-points targeting nuclear receptors (e.g. AhR, androgen receptor (AR), estrogen receptor (ER), farnesoid X receptor, peroxisome proliferator-activated receptor

(PPAR), pregnane X receptor (PXR), and retinoic acid receptor, among others) in cellular assays for transactivation, receptor dimerization, and nuclear translocation, as well as biochemical radioligand binding assays and coregulatory recruitment assays.

(9) *Causes immortalization*: 0 assay end-points.

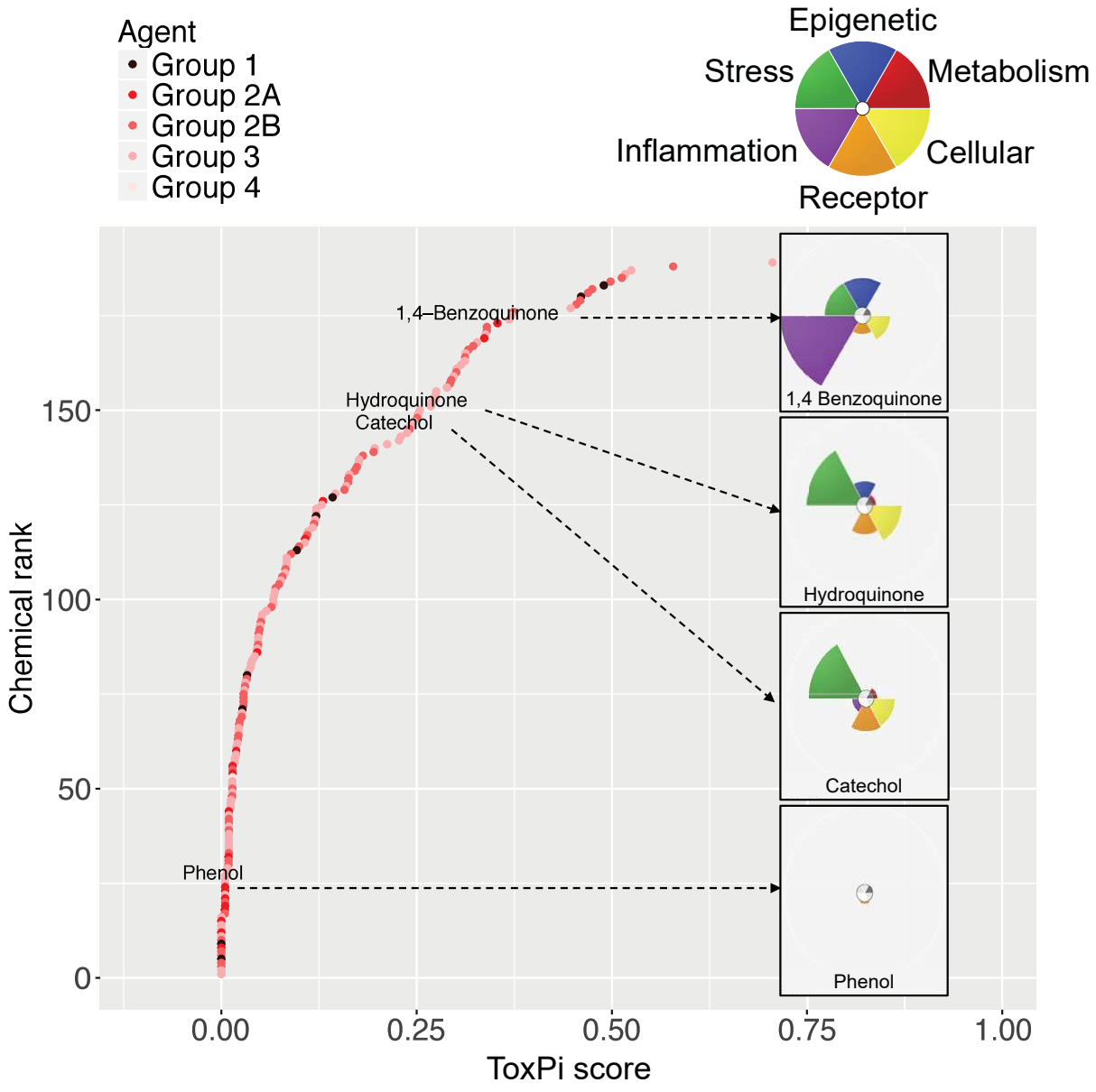
(10) *Alters cell proliferation, cell death, or nutrient supply*: 68 assay end-points measuring cell cycle markers, proliferation, cytotoxicity, and mitochondrial toxicity by a wide variety of assay formats in cell lines, primary human cells, and developing zebrafish larvae.

The activity of an agent on a given assay is determined by the statistical significance of the association between all tested concentrations of the agent with assay response (Sipes et al., 2013). The activity of each agent in each assay and across groups of assays was summarized using the Toxicological Prioritization Index (ToxPi) approach (Reif et al., 2010). In the Working Group's analysis, each agent–assay pair was summarized as "active" (1) or "inactive" (0). Within each key characteristic slice for a given agent, the distance from the origin represents the relative agent-elicited activity of the component assays (i.e. slices extending further from the origin were associated with "active" calls on more assays). The overall score of an agent is the aggregation of all slice-wise scores (Fig. 4.2, inset) and provides an activity ranking relative to the 189 agents screened in ToxCast/Tox21 that have been evaluated in the *IARC Monographs* (Fig. 4.3, rank chart).

A tabular and graphical summary of the results is given in the supplementary material (Annex 1), and a summary for each relevant compound follows. Note that the activity calls across these assays represent exposure to each of the four individual metabolites, and may not necessarily be indicative of exposure to benzene or its other metabolites.

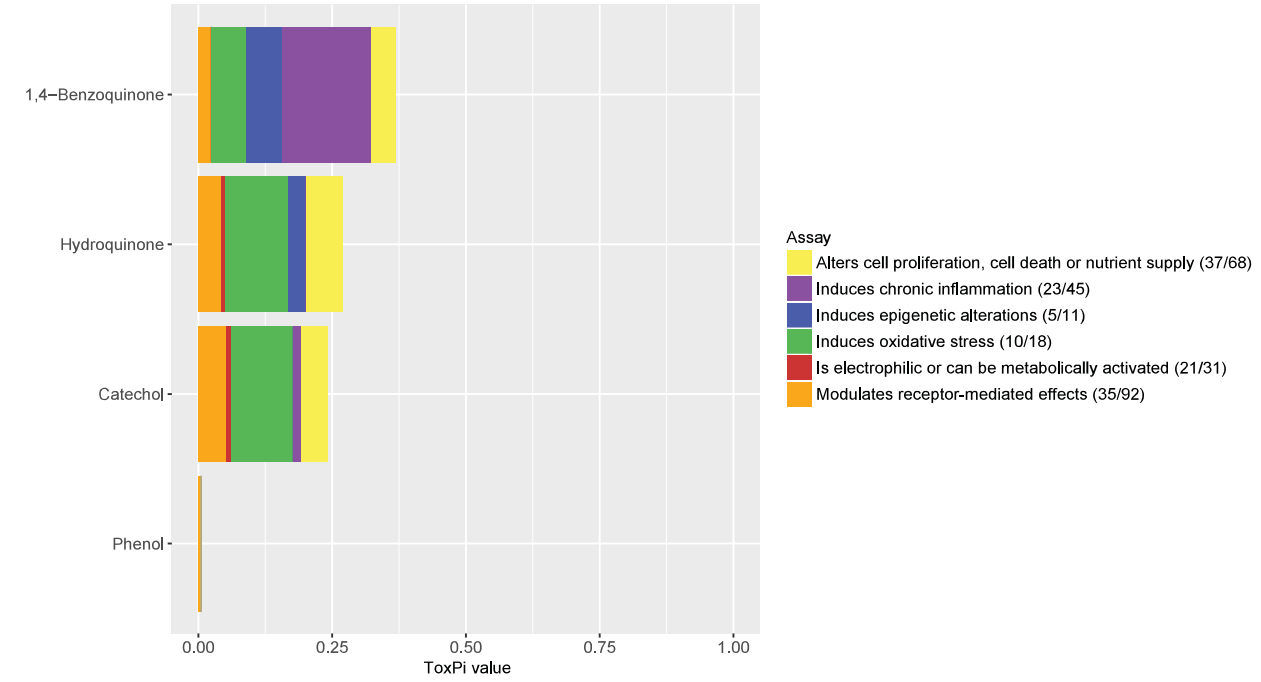
1,4-Benzoquinone (Chemical Abstracts Service, CAS, Registration No. 106-51-4) has the highest ToxPi value among the benzene metabolites evaluated, and has the 16th highest value among the 189 agents (16/189) evaluated by IARC (see Fig. 4.2). The largest contribution to this ToxPi value is from active hits to assays mapped to the "*Induces chronic inflammation*" category (Fig. 4.2). This represents the maximum number of hits to this category among the 189 evaluated IARC agents. Exposure results in upregulation of cell adhesion proteins E-selectin, P-selectin, and vascular cell adhesion molecule 1 (VCAM1), and in the upregulation of chemokines and cytokines such as CXCL9, CXC10, CCL2, IL-1a, IL-8, TNFα, CD38, CD40, and CD69 in multiple human cell cultures and co-cell cultures. NF-κb is also upregulated in the HepG2 cell line. The second-largest contributor to the ToxPi value derives from active hits mapped to the "*Induces epigenetic alterations*" category, with two hits out of four assays mapping to DNA binding (the seven assays associated with measuring chromatin alterations were not performed). Assays indicating upregulation of matrix metalloproteinase 1 in two cells cultures are linked to the "*Induces oxidative stress*" category, and the tissue inhibitor of metalloproteinases 2 is also upregulated in a co-culture involving one of the former lines. Assays suggesting upregulation of hypoxia-inducible factor-a and metal regulatory transcription factor-1 in HepG2 liver cell lines are also linked to 1,4-benzoquinone exposure. Hits associated with upregulation of six genes, including *TGFβ1*, *MYC*, and vascular endothelial growth factor *VEGFRII*, which are markers of cell-cycle across multiple platforms, downregulation of cellular proliferation across multiple cell-cultures as assayed by the sulforhodamine B colorimetric assay, and upregulation of two markers of cell proliferation were mapped to the "*Alters cell proliferation, cell death, or nutrient supply*" category. Upregulation of the gene expression of six receptors, including AhR, AR,

Fig. 4.2 ToxPi ranking for benzene metabolites phenol, catechol, hydroquinone, and 1,4-benzoquinone and all agents evaluated by IARC with available data using ToxCast and Tox21 assay end-points mapped to six key characteristics of carcinogens



Inset are the ToxPi diagrams for these metabolites. ToxPi diagram colour coding is provided in the legend. Each agent in the rank chart is plotted in a colour according to its IARC classification

Fig. 4.3 Stacked bar plots of ToxPi values by assay category for benzene metabolites phenol, catechol, hydroquinone, and 1,4-benzoquinone using ToxCast and Tox21 assay end-points mapped to six key characteristics of carcinogens



The numbers in the parentheses next to each category represent the ratio of the maximum number of hits to assays assigned to category over 189 IARC agents to the total number of assays assigned to the category

glucocorticoid receptor, and retinoid X receptor, all on the Attagene platform performed on HepG2 liver cell line, were linked to the "*Modulates receptor-mediated effects*" component of the ToxPi value.

Hydroquinone (CAS 123-31-9) has the second-highest ToxPi value of the benzene metabolites and the 39th highest ToxPi value among the 189 agents (39/189) evaluated by IARC (see Fig. 4.2). The largest contributor to this value came from active hits linked to the "*Induces oxidative stress*" category. This represents the ninth-highest number of hits to this category among the 189 evaluated IARC agents. This category contains assays mapped to regulation of matrix metalloproteinase 1 in one of the three cell cultures, regulation of oxidative stress and stress kinase after 72 hours of exposure, and four (hypoxia-inducible factor-a, metal regulatory transcription factor-1, nuclear erythroid-related factor-2, and antioxidant response element) out of six markers of oxidative stress measured in three separate assay platforms (Apredica, Attagene, and Tox21). The second-largest contributor came from hits linked to the "*Alters cell proliferation, cell death, or nutrient supply*" category, with indications of upregulation of cell cycle, downregulation of proliferation, and upregulation of mitochondrial toxicity. For assays assigned to "*Modulates receptor-mediated effects*" there are active hits for AhR, AR, glucocorticoid receptor, PPAR-response element, PXR-vitamin D response element, ER, and PPARγ. One out of the four assays associated with DNA binding (from the "*Induces epigenetic*

alterations" category) is active for hydroquinone exposure.

Catechol (CAS 120-80-9) has the third-highest ToxPi value of the benzene metabolites and the 45th highest ToxPi value among the 189 agents (45/189) evaluated by IARC (see Fig. 4.2). The largest contributor to this value came from the exact same active hits as for hydroquinone in assays linked to the "*Induces oxidative stress*" category. For assays assigned to "*Modulates receptor-mediated effects*" there are active hits for AhR, AR, ER, and PPAR. The assays linked to "*Alters cell proliferation, cell death, or nutrient supply*" category suggested upregulation of cell cycle and downregulation of proliferation across multiple cell cultures.

Phenol (CAS 108-95-2) was only active on a biochemical assay for ER, with no activity hits on any other assays assigned to the six categories of carcinogenicity.

In conclusion, 1,4-benzoquinone is the benzene metabolite most strongly associated with assays mapped to the six key characteristics of carcinogens, and with the "*Induces chronic inflammation*" category in particular. Hydroquinone and catechol showed a moderate number of hits. Phenol showed activity on only one assay. These four benzene metabolites were tested in different phases of the ToxCast or Tox21 programmes, resulting in different percentages of missing data (i.e. "not-tested" in a given assay). Relative to the full assay set, 1,4-benzoquinone was tested in 46% of all assays and catechol, hydroquinone, and phenol were tested in 88% of all assays. [The Working Group noted that a reanalysis of data, in which only assays with data for most of the full list of IARC chemicals tested were considered, resulted in similar ToxPi scores.]

4.4 Observed exposure–response relationships in mechanistic studies

Based on the *Report of the IARC Advisory Group to Recommend on Quantitative Risk Characterization* (IARC, 2014), a more detailed review of the availability of exposure–response information for mechanistic and other data from studies in exposed humans was performed. The purpose of this review was to explore the observed exposure–response relationships by summarizing information across studies on the magnitudes of response (e.g. relative percentage change) and the corresponding levels of exposure.

First, the representative studies of human benzene exposure that were the focus of Sections 4.1 and Section 4.2 relating to the key characteristics of carcinogens were further reviewed for availability of information relating level of exposure to degree of response. Only studies relating to key characteristics of carcinogens for which there was strong evidence in exposed humans were considered (see Section 5.4). Additional considerations for selecting studies included the availability of multiple exposure categories with associated measurements of benzene concentrations in air, adequate sample size, consideration of potentially confounding co-exposures, and/or completeness of reporting. Candidate studies were evaluated for their adequacy in terms of exposure assessment.

Based on these considerations, it was determined that exposure–response information was available for the key characteristics of carcinogens of "is genotoxic" and "is immunosuppressive", the second of which includes measures of haematotoxicity. Specifically, exposure–response information was available for the end-points for which there was strong evidence in exposed humans (see Section 5.4): (i) genotoxicity (oxidative DNA damage, indicated by 8-OHdG, and

chromosomal effects, indicated by MN and CAs); and (ii) immunosuppression and haematotoxicity (peripheral pluripotent stem cell and leukocyte counts).

Representative studies, independent of the presence or direction of a statistically significant effect, were then selected (see Section 4.2), and numbers in the exposed and reference groups, duration of exposure, and level of exposure among those exposed were examined. Further, for each end-point the measure of response, the evidence of an exposure–response gradient, the central tendency and measure of variance of end-point in the reference group, and the measure of exposure were all considered. Finally, considerations of each exposure category included: the central tendency and measure of variance of exposure; the central tendency of difference in response from the reference group as a percentage change (i.e. (mean of category – mean of the reference group)/mean of the reference group); and a test for significance of difference from the reference group (e.g. *t*-test) and *P* value.

[The Working Group noted that, because representative studies were selected, the existence of additional mechanistic studies with exposure–response information cannot be excluded. The possibility of publication bias on mechanistic end-points also cannot be excluded.]

4.4.1 Genotoxicity

Two studies with exposure–response information for oxidative DNA damage (8-OHdG) were selected (Lagorio et al., 1994; Liu et al., 1996). Both had statistically significant exposure–response trends, but the population in Lagorio et al. (1994) were exposed to benzene at much lower concentrations (mean, 0.45 mg/m^3 or 0.14 ppm) compared with those in Liu et al. (1996) (mean, 166.1 mg/m^3 or 51 ppm). Of the two studies, only the study conducted by Liu et al. (1996) divided exposed populations into categories; the group exposed to low concentrations (mean, 2.46 mg/m^3 or 0.76 ppm) was not statistically different, with an effect size of 25%, and the group exposed to medium concentrations (mean, 103.3 mg/m^3 or 31 ppm) was statistically significantly increased, with an effect size of 600%.

Four studies with exposure–response information for MN were selected (Liu et al., 1996; Rekhadevi et al., 2011; Zhang et al., 2014, 2016). [The Working Group noted that the study by Rekhadevi et al. (2011) was not informative for exposure–response because it had a narrow range of benzene exposures (1.1–1.5 mg/m^3 or 0.34–0.46 ppm) that was further divided into three categories.] All studies except for that of Rekhadevi et al. (2011) tested for exposure–response trends, all of which were statistically significant. Exposures in the Rekhadevi et al. (2011) (mean, 1.32 mg/m^3 or 0.41 ppm), Zhang et al. (2016) (median, 1.6 ppm), and Zhang et al. (2014) (median, 6.4 mg/m^3 or 2 ppm) studies were lower than those of the Liu et al. (1996) study (mean, 166.1 mg/m^3 or 51 ppm). Three of these studies divided exposed populations into categories that were compared with the reference group and, in each case, the group exposed to the lowest concentrations demonstrated a statistically significant increase in MN compared with the reference group, with effect sizes of 45–55% (Liu et al., 1996; Zhang et al., 2014, 2016).

Numerous publications with exposure–response information for CAs were selected (Bogadi-Sare et al., 1997; Zhang et al., 1998b, 2007, 2011, 2012b; Kim et al., 2004b; Xing et al., 2010; Rekhadevi et al., 2011; Marchetti et al., 2012), although many were of the same study population. All had statistically significant exposure–response trends with the exception of Rekhadevi et al. (2011) (see Working Group comment, above) and Bogadi-Sare et al. (1997). Exposure concentrations considered by Rekhadevi et al. (2011) (mean, 1.322 mg/m^3 or 0.41 ppm), Kim et al. (2004b) (geometric mean, 0.56 ppm), Marchetti et al. (2012) (mean, 2.8 ppm), Xing et al. (2010) (median, 2.9 ppm), and Bogadi-Sare et al. (1997)

(median, 5.9 ppm) were lower than those in the Zhang et al. studies (median, 10–31 ppm). Among the studies of exposure to lower concentrations, two divided exposed populations into categories that were compared with the reference group: Xing et al. (2010) and Marchetti et al. (2012). The response of the group exposed to the lowest concentration (median, 1.2 ppm) in the study by Marchetti et al. (2012) was statistically significantly different from the reference group, with an effect size of 33%. In the case of Xing et al. (2010), the group exposed to the lowest concentration (median, 1.0 ppm) was not statistically different with an effect size of 50%; the group exposed to the higher concentration (median, 7.7 ppm) was statistically significantly increased, with an effect size of 70%.

[The Working Group noted that, in the majority of studies examined, an exposure–response gradient between benzene exposure and both MN and CAs was reported.]

4.4.2 Immunosuppression and haematotoxicity

Numerous studies with exposure–response information for leukocyte counts were selected (Liu et al., 1996; Rothman et al., 1996; Ward et al., 1996; Qu et al., 2002; Lan et al., 2004; Robert Schnatter et al., 2010; Swaen et al., 2010; Zhang et al., 2016). All had statistically significant exposure–response trends with the exception of the study by Swaen et al. (2010), which was not statistically significant, and by Liu et al. (1996), in which no trend test was performed. Exposures in the studies by Swaen et al. (2010) (mean, 0.22 ppm), Zhang et al. (2016) (median, 1.6 ppm), Robert Schnatter et al. (2010) (median, 2.3 ppm), Qu et al. (2002) (mean, 3.8 ppm), and Lan et al. (2004) (mean, 5.1 ppm) were lower than in the studies by Rothman et al. (1996) (median, 31 ppm) and Liu et al. (1996) (mean, 166.1 mg/m^3 or 51 ppm). Ward et al. (1996) only reported the maximum exposure level (34 ppm).

Six studies divided exposed populations into categories (Liu et al., 1996; Rothman et al., 1996; Qu et al., 2002; Lan et al., 2004; Swaen et al., 2010; Zhang et al., 2016). The groups exposed to the lowest concentrations in these studies had effect sizes ranging from a 0.8% increase to a 14.5% decrease in leukocytes, with the effects observed in Lan et al. (2004) (14.5% decrease at a mean exposure of 0.57 ppm) and Qu et al. (2002) (4.3% decrease at a mean exposure of 3.07 ppm) being statistically significant. In the case of Swaen et al. (2010), none of the groups (< 0.5 ppm, 0.5–1.0 ppm, > 1.0 ppm) demonstrated statistically significant changes (effects ranging from 1% increase to 1% decrease). In Zhang et al. (2016), the groups exposed to the two lowest concentrations (3.55 ppm-yr and 6.51 ppm-yr) had non-significant decreases of 5.3%, whereas the third exposure group (10.72 ppm-yr) had a significant decrease of 11.2%. In Liu et al. (1996), the lowest exposure category (mean, 2.46 mg/m^3 or 0.76 ppm) demonstrated a 0% change, but the middle exposure category (mean, 103.3 mg/m^3 or 31 ppm) showed a 17% decrease (no statistical tests were performed). In Rothman et al. (1996), the group exposed to the lower concentration (median, 13.6 ppm) demonstrated a non-significant decrease of 5.8%, whereas the group exposed to the higher concentration (median, 91.9 ppm) had a significant decrease of 17.6%.

[The Working Group noted that, in the majority of studies examined, an exposure–response gradient between exposure to benzene and leukocyte count was reported. Some other studies discussed in Section 4.2.4(a), which evaluated populations exposed to relatively low levels of benzene, reported no effects on leukocytes; these studies are not included here, however, because they were not informative for exposure–response analyses (e.g. they only compared all levels of exposure with the reference group).]

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