DEVELOPMENT OF A DATABASE OF KEY CHARACTERISTICS OF HUMAN CARCINOGENS

Supplemental Material I: Toxicological Endpoints Expressed by Six Group-1 Agents

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The key characteristics of the 86 Group-1 agents considered by Birkett et al. (2019) were determined based on the corresponding toxicological endpoints expressed by those agents, by use of the mapping of these endpoints to the key charcteristics given in Table 2. The determination of key characteristics for the six agents summarized in Table 3 is described in detail below.

References in the main text below were drawn from the *Monographs* themselves and from relevant literature published around the time of their publication. In the 'Updated PubMed search', more recent studies are cited to support the identification of TEs and the ensuing KCs. In some cases, this search revealed information that led to novel TE/KC assignments. Details on the numbering of the 24 TEs and their categorization in terms of the ten KCs are given elsewhere in this Annex (Tables 1–2).

Tamoxifen (IARC, 2012a)

Tamoxifen induces DNA damage (TE#1). DNA adducts were detected in some studies in endometrial tissue and in leukocytes of breast-cancer patients treated with tamoxifen (Hemminki et al., 1996; Shibutani et al., 1999; Umemoto et al., 2004). DNA adducts were also found in animals in vivo (Davies et al., 1997; Tryndyak et al., 2006; Gamboa da Costa et al., 2007) as well as in vitro in mammalian cells (Glatt et al., 1998). Tamoxifen induced DNA double-strand breaks and oxidized purines and pyrimidines via formation of free radicals (TE#2) in human peripheral blood lymphocytes and in human MCF-7 breast cancer cells (Wozniak et al., 2007). Clastogenic effects (TE#4) of tamoxifen were shown as formation of micronuclei in human lymphoblastoid MCL-5 cells (Styles et al., 1997), and of chromosome aberrations and micronuclei in vivo in mouse bone marrow (Vijayalaxmi & Rai, 1996; Hirsimäki et al., 2002) and in rat liver (Styles et al., 1997). Tamoxifen also induced endometrial *K-RAS* mutations (TE#5) in postmenopausal breast cancer patients (Wallén et al., 2005), and it reduced p53 protein levels in MCF-7 human breast adenocarcinoma cells (Guillot et al., 1996). Tamoxifen also acts through epigenetic mechanisms (TE#6). Methylation of cell-free plasma DNA of breast cancer patients was altered after treatment with the agent (Liggett et al., 2011). Treatment of human endometrial cell cultures with tamoxifen resulted in changes in expression of genes associated with transcription regulation, cell-cycle control and signal transduction (Pole et al., 2005). In endometrial epithelial cells,

the gene PAX2 is crucially involved in cell proliferation and endometrial carcinogenesis; this gene is activated by tamoxifen via hypo-methylation of its promoter (Wu et al., 2005b). Long-term exposure of rats to tamoxifen induced histone modifications (Tryndyak et al., 2006) and led to substantial changes in expression of microRNA genes in the liver (Pogribny et al., 2007).

Tamoxifen is an anti-estrogen that acts, at least in part, by competing with estrogen receptors (TE#17). It is thus effective in arresting the growth of estrogen-responsive tumour cells. However, tamoxifen also inhibited the growth of MDA-MB-435 human breast cancer cells (Charlier et al., 1995) and of A549 human lung adenocarcinoma cells (Croxtall et al., 1994), which are both ER-negative. Apparently, ER-independent mechanisms are operative here (Reddel et al., 1985; Naundorf et al., 1996).

Tamoxifen induced an imbalance between cell proliferation (TE#15) and apoptosis (TE#13), as was shown in benign endometrial tissue from tamoxifen-treated breast cancer patients (Mourits et al., 2002). Estrogen modulators – including tamoxifen – affected transduction of cellular signalling pathways that govern cell growth and proliferation, through downstream effectors such as PAX2 (Shang, 2006). Tamoxifen reduced cell proliferation (TE#15) in human MCF-7 and MDA-MB-231 breast carcinoma cells, and induced changes in the expression of individual telomerase components (TE#20), which correlated with telomerase activity and cell proliferation (Aldous et al., 1999). Tamoxifen inhibited the growth of human MCF-7 breast cancer cells, as well as the expression of telomerase reverse transcriptase (hTERT), but it stimulated the growth and activated hTERT mRNA expression in human endometrial carcinoma cells. These effects of tamoxifen are mediated by transcriptional regulation of the hTERT promoter (Wang et al., 2002a). The tamoxifen-induced decrease of telomerase activity in human HepG2 hepatoblastoma cells was shown to be mediated by post-translational suppression of protein kinase C activity (Brandt et al., 2005).

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Tamoxifen induces oxidative stress (TE#2). In cells derived from the human retinal pigment epithelium and from the mouse retinal photoreceptor, tamoxifen-induced cell death was accompanied by increased oxidative stress and elevated zinc levels; this effect was attenuated by the antioxidant *N*-acetyl-L-cysteine (Cho et al., 2012). Rats treated with tamoxifen showed an increase in aminotransferases, carbonyl groups and 8-oxo-dG, all markers of oxidative stress (Codoñer-Franch et al., 2013). Tamoxifen caused autophagic cell death of human glioma cells in vitro through induction of oxidative stress, JNK activation, and up/downregulation of pro/anti-autophagic members of the BCL2 family (Harmalkar et al., 2015). Tamoxifen induced a significant reduction in fat mass in adipose mice and transiently stimulated the production of reactive oxygen species (ROS) in these mice, and in murine adipocytes exposed to tamoxifen in vitro (Liu et al., 2015). The growth-inhibitory effects of tamoxifen on MCF7 human breast cancer cells were associated with enhanced levels of ROS production and lipid peroxidation (Sajadimajd et al., 2016).

Hepatitis B virus (IARC, 2012b)

Hepatitis B virus (HBV) induces chronic necro-inflammatory hepatic diseases (cirrhosis, chronic hepatitis) characterized by necrosis of hepatocytes followed by regenerative cell proliferation. These disorders induce oxidative/nitrosative stress and lipid peroxidation (LPO), thereby generating excess reactive oxygen species (ROS), reactive nitrogen species (RNS), and DNA-reactive aldehydes. The DNA adduct (TE#2) etheno-deoxyadenosine – resulting from interaction with LPO-generated aldehydes – was excreted in urine of HBV-infected patients diagnosed with chronic hepatitis, cirrhosis and hepatocellular carcinoma (Bartsch & Nair, 2004; Bartsch & Nair, 2006). The HBV-encoded X protein (HBx) increased the level of mitochondrial reactive oxygen species (TE#2) and caused lipid peroxide production in human liver cells (Lee et al., 2004). In human HepAD38 hepatoma cells in vitro, HBV replication induced oxidative stress and caused upregulation of heat-shock proteins and of genes (TE#7) associated with oxidative and metabolic stress, cell growth, and apoptosis (Severi et al., 2006).

Oxidative stress and oxidative DNA damage were also observed in hepatocytes of transgenic mice overexpressing the HBV large envelope protein (Hagen et al., 1994) or the HBx protein (Gehrke et al., 2004). The HBx protein modulates DNA-repair processes (TE#16) by interacting with p53 and/or repair enzymes, which may accumulate mutations (TE#5) and sensitize cells to genotoxic stimuli (Murakami, 1999). In transfection experiments with human HepG2 hepatoma cells, this protein was also found to trans-activate the *c-MYC* proto-oncogene at the transcriptional level (Balsano et al., 1991).

HBV infection causes clastogenic/cytogenetic effects (TE#4). Analysis of hepatocellular carcinoma (HCC) tissue showed that integration of HBV DNA caused secondary chromosomal rearrangements, such as translocations, inversions, deletions and (possibly) amplifications (Matsubara & Tokino 1990). Chromosome abnormalities were detected in peripheral blood cells of HBV chronic carriers (Simon et al., 1991). Increased frequencies of chromosomal alterations and micronuclei were found in human hepatoma HepG2 cells transfected with the HBX gene (Livezey et al., 2002), as well as in HBV carriers and HBV patients (Leite et al., 2014). HBV-transfected HepG2T14.1 cells (variant of the HepG2 cell line) showed several genetic alterations such as de-novo aberrations of chromosomes 9, 14, 15, and 20, as well as loss of heterozygosity (LOH) in the q region of chromosome 14. In HBV chronic carriers and HBV-positive patients with cirrhosis, the frequency of sister chromatid exchange (SCE) was significantly higher than in the controls (Ucur et al., 2003).

HBV also acts via epigenetic mechanisms (TE#6). HCC tissue samples showed higher methylation frequencies in several genes, e.g. APC, GSTP1, Cox-2, than did samples from non-HCC liver tissue (Lee et al., 2003; Oh et al., 2007; Su et al., 2007). In human HepG2 and Huh7 hepatoma cells in vitro, HBV replication induced methylation of both host and viral DNA (Vivekanandan et al., 2010). The HBx protein promoted regional hyper-methylation and global hypo-methylation in cultured human liver cells (Park et al., 2007), and in HCC cells (Jung et al., 2010). Differential microRNA expression was observed in liver tissue obtained from 12 patients with HBV-related HCC; analysis of targeted genes by use of these infection-associated miRNAs revealed that pathways related to cell death, DNA damage, recombination, and signal transduction were activated in HBV-infected liver (Ura et al., 2009). Deregulation of miRNA was an early event and accumulated throughout the various steps of HBV-associated hepatocarcinogenesis, with miRNA-145 being a candidate tumour-suppressive miRNA with an important role in HCC development (Gao et al., 2011). Similar effects of differential miRNA expression during acute and chronic infection were found in HBV-transfected HepG2 cells (Zhang et al., 2011). HBV replication in human HuH7 hepatoma cells and in liver tissue from HBV-infected patients was shown to be regulated by the acetylation status of the H3/H4 histones bound to the HBV mini-chromosome (Pollicino et al., 2006).

HBV also induces changes in gene expression (TE#7). In HCC tissues/cell lines, HBV was found to be integrated into hepatocellular genomic DNA and shown to encode transcriptional trans-activators that stimulate gene expression from homologous and heterologous promoters (Schlüter et al., 1994). HBV-DNA integration sites isolated from HCC tissue showed that the viral genome induced mutations in key regulatory cellular genes (TE#5) (Paterlini-Bréchot et al., 2003). Integration of the HBV X DNA fragment and changes in gene expression were also seen in archival HCC specimens obtained from patients with HBV infection (Peng et al., 2005). In HepG2 cells, transfection with HBx induced expression of key genes involved in modulating signal-transduction pathways (Cougot et al., 2007).

HBV induces changes in cell signalling (TE#8). In HepG2 and HuH7 human hepatoma cells, the HBx protein, encoded by the HBX gene, induced cytoplasmic retention of the p53 protein (Takada et al., 1997). This same protein also induced expression of key factors involved in complex signal-transduction pathways for transactivation, through interaction with binding sites for transcription factors AP-1, AP-2, and NF-kappa B (Kekulé et al., 1993). The HBx protein induced expression of genes encoding metastasis-associated protein 1 and histone deacetylase in HCC, and in the liver of HBx-transgenic mice (Yoo et al., 2008).

HBV induces acute and chronic inflammation (TE#12) (Bertoletti & Gehring, 2006) The HBV-specific e-antigen (HBeAg) was shown to have an important immunomodulatory role in this process, playing a part in inflammation and regulation of the immune response during acute and chronic HBV infection (Yang et al., 2006).

Integration of the HBV X DNA fragment in HCC modulates the expression of multiple molecules that play a key part in cell-cycle regulation (TE#15), apoptosis (TE#13), and cell proliferation, as was found in samples from HCC patients with HBV infection (Peng et al., 2005). The protein HBSP is generated by splicing during natural HBV infection. Interaction of its BH3 (Bcl2-homology) domain with Bcl-2/Bcl-x1 was sufficient to induce apoptosis in HepG2 cells (Lu et al., 2006; Lu et al., 2008). Expression of HBx in transgenic mice elicited an apoptotic response in the liver, independent of functional p53 protein. A direct, dose-dependent apoptotic function of HBx was also demonstrated during transient transfection of hepatocytes in vitro (Terradillos et al., 1998). The same protein was able to induce proliferation of human and animal hepatocytes in vitro and of hepatocytes in animals in vivo (Madden & Slagle 2001), but this pleiotropic protein also inhibited liver regeneration in animals in vivo and in animal cells in vitro (Tralhao et al., 2002). In a later study, HBx was shown to be either pro-apoptotic or anti-apoptotic in primary rat hepatocytes, depending on the status of NF-kappaB: when HBx-induced activation of NF-kappaB was blocked, HBx stimulated apoptosis (Clippinger et al., 2009). This protein inhibited the growth of HCC cells and induced G2/M arrest in vitro and in vivo by persistent activation of the cyclin B1-CDK1 kinase (Cheng et al., 2009). In contrast, HBx promoted proliferation and upregulated transforming growth factors and connective tissue growth factors in a human hepatic stellate cell line (Guo et al., 2009a). The HBx protein also interfered with DNA repair (TE#16) in human hepatoma cells and fibroblasts in vitro (Becker et al., 1998), and downregulated XPB (i.e. ERCC3) and XPD (i.e. ERCC2), two important components of the transcription-repair factor TFIIH in human hepatoma cells (Qadri et al., 1996; Jaitovich-Groisman et al., 2001). The HBx protein repressed transcription of insulin-like growth factor binding protein-3 (IGFBP-3) by forming a complex with histone deacetylase 1 (Shon et al., 2009).

In HCC tissues harbouring HBV, shortening of the restriction fragments (TRFs) at the ends of telomeres was demonstrated (TE#20) (Ohashi et al., 1996). Analysis of HBV-DNA integration sites isolated from different HCCs showed that the viral genome acted as an 'insertional mutagene', causing mutations in important genes controlling cell growth, which may lead to oncogenic transformation (TE#23) (Paterlini-Bréchot et al., 2003). In HCC-derived cell lines, the HBV-DNA integrates in a liver-DNA sequence that strongly resembles that of the oncogene v-ERB-A, thus contributing to cell transformation (Dejean et al., 1986).

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HBx induced repression of the human E-cadherin gene through histone deacetylation in cultured human HepG2X hepatoma cells, stably transfected with HBx (Arzumanyan et al., 2012). HBV induced acute and chronic inflammation (TE#12) (Fallot et al., 2012). HBx activities in biologically relevant hepatocyte systems provided a link between modulation of apoptotic pathways by HBx (TE#13) and the development of HBV-associated HCC (Rawat et al. 2012). A meta-analysis of case–control studies demonstrated that polymorphisms in genes encoding microRNAs 146a and 196a-2 were associated with susceptibility to HBV-induced hepatocellular carcinoma (Xu et al., 2013a). HBx regulated numerous cellular signal-transduction pathways and transcription factors as well as cell-cycle progression and apoptosis (Xu et al., 2014a).

Arsenic (IARC, 2012c)

In cultured human alveolar type II (L-132) cells, dimethylarsinic acid caused single-strand DNA breaks and suppressed replicative DNA synthesis (TE#1) (Tezuka et al., 1993). Inorganic and organic (methylated) arsenic compounds induced DNA strand breaks in human blood cell lines, possibly by

different mechanisms (Wang et al., 2002a). In cultured human HeLa S3 cells, arsenite and its methylated metabolites induced high levels of oxidative DNA damage (TE#2) (Schwerdtle et al., 2003). Sodium arsenite in drinking-water caused oxidative stress in liver, brain and erythrocytes of rats (Flora 1999).

Arsenic also induces cytogenetic damage (TE#4). Increased frequencies of chromosomal aberrations and sister chromatid exchange were observed in humans exposed to inorganic arsenic in drinking-water (Mahata et al., 2004). Chromosomal aberrations (Oya-Ohta et al., 1996) and micronuclei (Yih & Lee 1999) were found in human fibroblasts exposed to arsenicals in vitro. Arsenic also induced formation of micronuclei, in bone marrow of exposed mice (Deknudt et al., 1986; Lewińska et al., 2007). In vitro, it induced micronucleus formation in Chinese hamster V79 lung fibroblasts (Sinha et al., 2005). The mono- and dimethylated metabolites of trivalent arsenic were clastogenic (TE#4) in human lymphocytes and mutagenic (TE#5) in mouse lymphoma cells in vitro, but were negative for gene mutation in three strains of Salmonella typhimurium in the plate-incorporation assay (Kligerman et al., 2003). In the Drosophila melanogaster wing somatic mutation and recombination test (SMART) – which measures loss of heterozygosity resulting from gene mutation, chromosome rearrangement, breakage, and loss – the organic arsenic compound dimethylarsinic acid (DMAV) increased the frequency of mutant spots; inorganic arsenic was inactive in this assay (Rizki et al., 2006). Arsenite acted as a co-mutagen at the hypoxanthine-guanine phosphoribosyl-transferase (Hprt) locus in Chinese hamster V79 lung fibroblasts irradiated with UV light of three different wavelengths (Li & Rossman 1991). In-vitro treatment of Chinese hamster cells with sodium arsenite caused genetic instability (micronucleated, multinucleated, and apoptotic cells) (TE#16), aneuploidy, and persistent genome-wide hypomethylation (TE#6) (Sciandrello et al., 2002; Sciandrello et al., 2004).

Arsenic-induced carcinogenesis may proceed through epigenetic mechanisms (TE#6). The promoter regions of the genes TP53 and CDKN2A (encoding the tumour-suppressor protein p16) were hypermethylated in people chronically exposed to arsenic and in subjects with arsenic-related skin cancer (Chanda et al., 2006). Arsenic also induced specific alterations in histone H3 methylation in human A549 lung carcinoma cells (Zhou et al., 2008). As mentioned above, genome-wide hypomethylation was observed in V79-Cl3 Chinese hamster cells treated with arsenite (Sciandrello et al., 2004). Arsenic also induced changes in histone H3 acetylation and DNA methylation in human urothelial cell lines (Jensen et al., 2008) and alterations in cellular micro-RNA expression profiles in human lymphoblastoid cells (Marsit et al., 2006).

Arsenite induced amplification (TE#7) of the dihydrofolate reductase (*Dhfr*) gene in 3T6 mouse embryo fibroblasts, which became methotrexate-resistant (Lee et al., 1988), and also amplified DHFR in human osteosarcoma TE85 (HOS) cells (Mure et al., 2003).

Arsenic may induce altered cell signalling (TE#8), especially at low doses. Treatment of human keratinocytes and fibroblasts with 0.1–1 microM arsenic increased transcription, protein levels and enzyme activity of several base-excision repair genes, including DNA polymerase beta and DNA ligase I. However, at higher concentrations (> 10 microM), arsenic induced downregulation of DNA repair, oxidative DNA damage and apoptosis (Snow et al., 2005).

Developmental stage-dependent susceptibility (TE#10) to the effects of arsenic was studied in newborns whose mothers experienced varying levels of arsenic exposure during pregnancy. Gene-expression profiling identified 11 activated transcripts associated with activation of molecular networks involving NF-kappaB, stress, inflammation (TE#12), cell proliferation, and apoptosis in the newborn (Fry et al., 2007).

Arsenic induced oxidant stress and NF-kappa B activation in cultured aortic porcine endothelial cells, with superoxide and hydrogen peroxide being the predominant reactive species that stimulate cell signalling and activate transcription factors (Barchowsky et al., 1996; Barchowsky et al., 1999). Long-term, low-dose exposure to arsenic induced a generalized resistance to apoptosis in cultured HaCaT human keratinocytes, which then became tolerant toward high doses of arsenic, UVA radiation, and a number of chemotherapeuticals (Pi et al., 2005). Pretreatment of human keratinocytes with sodium

arsenite in vitro decreased the pro-apoptotic effects (TE#13) induced by UVB (Chen et al., 2005). Sodium arsenite inhibited apoptosis induced by UVR (solar-simulation ultraviolet radiation) in mouse keratinocytes (Wu et al., 2005b).

Arsenic interferes with cell proliferation and differentiation (TE#15), as evidenced by stimulation of keratinocyte-derived growth factors in primary human epidermal keratinocytes (Germolec et al., 1997), by an increase in cyclin D1 in normal human fibroblasts (Vogt & Rossman 2001), as well as by K-RAS oncogene overexpression and hypomethylation of genomic DNA in prostatic epithelial cells (Benbrahim-Tallaa et al., 2005a). Increased proliferation of the bladder epithelium was observed in mice exposed to arsenite in drinking-water (Luster & Simeonova, 2004). Cell proliferation was also induced in animal cells (Trouba et al., 2000) and in human cells (Komissarova et al., 2005) treated with arsenic in vitro.

Arsenic also interferes with cellular DNA repair (Hartwig & Schwerdtle 2002) (TE#16). Exposure to trivalent mono-methyl arsenic strongly inhibited DNA repair in normal human primary fibroblasts by reducing TP53 induction after exposure to a carcinogen (Shen et al., 2008) or by inhibition of poly(ADP-ribosyl)ation in cultured human HeLa S3 cells (Walter et al., 2007). These studies also indicated that inhibition of DNA repair by arsenic contributed to genomic instability. Sodium arsenite was co-mutagenic with N-methyl-N-nitrosourea (MMU) at the *Hprt* locus in V79 Chinese hamster lung fibroblasts, probably by inhibiting proper repair of MNU-induced DNA lesions or by interfering with DNA-ligase activity (Li & Rossman 1989).

Arsenic exhibits receptor-mediated effects (TE#17). Chronic exposure to arsenic induced androgen independence in human prostate epithelial cells. This malignant transformation led to a sixfold increase in the expression of the *K-RAS* oncogene (Benbrahim-Tallaa et al., 2005b; Benbrahim-Tallaa et al., 2007). Arsenite and arsenate activated extracellular signal-regulated kinases 1/2 by an epidermal growth factor receptor-mediated pathway in normal human keratinocytes (Tanaka-Kagawa et al., 2003). Arsenic is a potent endocrine disruptor, altering gene regulation by the closely related steroid hormone receptors for glucocorticoids (GRs), mineralocorticoids (MRs), progesterone (PR), and androgen (AR) in a similar manner (Davey et al., 2007).

Angiogenic effects (TE#19) of arsenic were demonstrated in the chick chorioallantoic membrane (CAM) model: exposure to sodium arsenite (33 nM) caused a twofold increase in blood vessel branching (Mousa et al., 2007). In mice, low levels of arsenic (50–500 ppb in drinking-water) stimulated inflammatory angiogenesis and blood-vessel remodeling in the liver (Straub et al., 2007; States et al., 2009).

As evidence for immortalization (TE#23), sodium arsenite and sodium arsenate induced neoplastic transformation in normal, diploid Syrian hamster embryo (SHE) cells (Takahashi et al., 2002). Inorganic arsenite induced malignant transformation of human prostate epithelial cells (Achanzar et al., 2002).

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Arsenic induced chromosomal aberrations and micronuclei (TE#4) in bone-marrow cells of rats (Patlolla et al., 2012), and erythrocytes of mice (Khan et al., 2013). Arsenic trioxide and sodium arsenite inhibited growth and induced death of P3HR1 lymphoblastoid cells: arsenite induced caspase-dependent apoptosis (TE#13) whereas arsenic trioxide triggered autophagic cell death (Zebboudj et al., 2014). Upon acute or chronic exposure to arsenite, human bronchial epithelial cells overexpressed the cytokines IL-6 and IL-8, which were essential for the progression of the arsenite-induced transformation of these cells. These data reveal a link between inflammation (TE#12) and malignant transformation (TE#23) in cells chronically exposed to arsenite (Xu et al., 2013b). In acute promyelocytic NB4 leukaemia cells, arsenic trioxide caused an increase in the expression (TE#7) of CDKN1B (encoding the p27 cyclin-dependent kinase inhibitor) and CDKN2A (encoding protein p16), and a reduction in the expression (TE#7) of hTERT (telomerase reverse transcriptase) (Yaghmaie et al., 2012).

UV and Solar Radiation (IARC, 2012d)

Ultraviolet (UV) light is a genotoxic agent (TE#1) (Griffiths et al., 1998). UV radiation and visible light (290–500nm) induced DNA damage (TE#1) in cultured AS52 Chinese hamster ovary (CHO) cells (Kielbassa et al., 1997). Radiation in the UVA region (315–400nm) is only weakly absorbed by DNA, and induction of DNA damage occurs largely via photosensitizers that absorb UVA and release reactive oxygen/nitrogen species (ROS/RNS) that mediate DNA-damage induction (Ridley et al., 2009). Exposure of sea-urchin embryos to UVB (290–320nm) resulted in significant DNA damage measured as cyclobutane pyrimidine dimers (CPD), followed by a cascade of cellular events, and eventually apoptosis (Lesser et al., 2003). UVA (320–340nm) induced formation of single-strand breaks, oxidized pyrimidines, oxidized purines (essentially 8-oxo-7,8-dihydroguanine), and CPDs (largely TT-dimers) in CHO cells (Douki et al., 2003), and DNA strand-breaks in human HaCaT skin keratinocytes (Didier et al., 1999). UVA induced formation of reactive oxygen species (TE#2) in human keratinocytes, in particular after replacement of cholesterol with the more rapidly oxidized dehydrocholesterol (Valencia et al., 2006). Oxidative lesions in DNA were found in human skin fibroblasts and keratinocytes exposed to UVA radiation (Courdavault et al., 2004; Mouret et al., 2006), although CPDs predominated.

UV radiation causes cytogenetic effects (TE#4). UVB (302nm) induced chromatid breaks in primary human lymphocytes in vitro (Wang et al., 2005). UVB (310–315nm) induced DNA strand-breaks in JB6 mouse epidermal cells; addition of various antioxidant enzymes revealed that this DNA breakage is at least in part mediated by the formation of hydrogen peroxide and possibly other reactive species (Ghosh et al., 1993). In cultured CHO cells, 254-nm low-intensity continuous wave UV light strongly enhanced the level of sister chromatic exchange (SCE) (Rasmussen et al., 1989). UVA radiation (330–400nm) caused DNA strand-breaks and chromosomal aberrations in human HaCaT cells (Wischermann et al., 2008).

UV and solar radiation are capable of inducing gene mutation (TE#5) (Pfeifer et al., 2005). In skin tumours from Xeroderma pigmentosum (XP) patients, all mutations in the TP53 gene were targeted at bi-pyrimidine (py-py) sequences, 55% of which were tandem CC→TT transitions, which are considered to be a signature of exposure to UV (Dumaz et al., 1994). Likewise, nearly all the melanomas from XP patients who carried mutations in the PTEN tumour-suppressor gene had several UV-associated mutations, occurring at adjacent pyrimidines (Wang et al., 2009). Fingerprint mutations for UVA (AT > GC transversions) and UVB (GC > AT transitions) at py-py sites were analysed in the *TP53* gene in human skin squamous cell carcinoma (SCC) and solar keratosis (SK) samples. These two mutation types occurred in nearly equal numbers, with UVA fingerprints largely distributed in the basal layer and UVB-induced mutations mainly in the supra-basal region (Agar et al., 2004). Clones of TP53-mutated cells were present in normal human and murine epidermis exposed to UVB, with sunlight acting as a tumour promoter by favouring the clonal expansion of TP53-mutated cells (Wikonkal & Brash 1999). Half of the skin tumours induced in hairless SKH/HR1 mice by daily exposure to long-wave UVA (365nm) showed positive staining for the p53 protein, and about 15% of the tumours showed a mutation in one of the exons 5, 7, or 8 of the p53 gene; no UVA-specific mutations, i.e. mutations specific for reactive oxygen species, were detected (van Kranen et al., 1997). Similarly, UV-signature mutations in the p53 tumour-suppressor gene are normally found in squamous cell carcinoma of experimental animal models (Rass & Reichrath 2008). When human 293-GTI-K embryonic kidney cells, which carry the lacZ bacterial gene on a stable shuttle vector, were irradiated with UVA or UVB, similar frequencies of LacZ mutations were seen at > 10% cell survival, whereas UVA induced twice as many mutations as did UVB at < 10% survival; mutations at A/T base pairs were induced more frequently by UVA than by UVB (Robert et al., 1996). In a series of human skin tumours, over 90% of squamous cell carcinomas and more than 50% of basal cell carcinomas contained UV-like mutations in the TP53 tumour suppressor gene. The DNA lesions were pyrimidine-cytosine photoproducts caused by the UVB component of sunlight. Particular codons of the TP53 gene are most susceptible, apparently because of slower DNA repair at specific sites (Brash et al., 1996).

Continuous UV radiation at 254 nm was mutagenic in CHO cells at the ouabain resistance locus Ouar and at the Hgprt gene locus (Rasmussen et al., 1989). UVA-induced CPDs were found predominantly at T-T dipyrimidines and correlated with the mutation spectrum (C→T and CC→TT transitions) in CHO cells (Rochette et al., 2003).

UV radiation can give rise to epigenetic changes (TE#6). UV radiation induced DNA hypermethylation and histone hypo-acetylation in human SCC cells in vivo and in SKH-1 hairless mice in vivo (Nandakumar et al., 2011). Aberrant methylation of tumour-suppressor gene promoters associated with transcriptional downregulation was shown in UV-induced human skin tumours such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), melanoma, and cutaneous lymphoma (van Doorn et al., 2005). UV radiation induced histone modifications in human skin fibroblasts in vitro (Kim et al., 2009a) and in the skin of hairless mice (Kim et al., 2013). Differential microRNA expression profiles have been described in NIH3T3 mouse embryo fibroblasts (Guo et al., 2009b) and in human keratinocytes (Zhou et al., 2012) in response to irradiation with UVB.

UV radiation also induces changes in gene expression (TE#7) in human cells in vivo (Rochette et al., 2009) as well as in vitro (Koch-Paiz et al., 2004; He et al., 2006). In human skin fibroblasts, repeated non-cytotoxic UVB exposures induced premature senescence, with loss of replicative potential and overexpression of senescence-associated genes (Chen et al., 2008). UV radiation induced prostaglandin E2 production and COX-2 expression in human skin in vivo (Seo et al., 2003), indicating that it can interfere with cell-signalling pathways (TE#8).

Genotype susceptibility (TE#10) to UV-induced skin cancer has been reported in vivo in human melanoma skin cancers: following exposure to UVB, methylated cytosines were significantly more susceptible to CPD formation than unmethylated cytosines (Rochette et al., 2009; 19 427 505). UV-induced changes in tyrosine cell signalling in melanocytes, keratinocytes, and fibroblasts from both human and murine sources were dependent on the characteristic genotypes of the cells exposed: UVR induced the receptor tyrosine kinase EphA2 by a p53-independent, but MAPK-dependent, mechanism (Zhang et al., 2008). Young adult BALB/c mice were more susceptible to the induction of skin tumours from FS40 sunlamps (emitting mainly UVB) than were 18-month-old animals (Ebbesen & Kripke 1982). Exposure to high levels of sunlight in childhood is a strong determinant of melanoma risk, which indicates developmental stage susceptibility to UV-induced cancers (Whiteman et al., 2001).

UV induces immunosuppression and immunomodulation (TE#11) in exposed humans. Solar-simulated UV caused significant immunosuppression in human volunteers, but equivalent doses of UVB and UVA did not, when given independently (Damian et al., 2008). However, interactions between UVA and UVB augment each other, enabling immunosuppression to occur at doses too low for either waveband to be suppressive (Halliday & Rana 2008). UVB radiation can alter the secretion of cytokines by epidermal keratinocytes and dermal fibroblasts (Fujisawa et al., 1997). These alterations have been implicated in UVB-induced immunosuppression and UVB-induced carcinogenesis (Eberlein-König et al., 1998; Suzuki et al., 2001).

In mice, chronic irradiation with UV produced a systemic change in the immune defence (TE#11), which resulted in the failure of the UV-irradiated mice to reject highly antigenic, transplanted UV-induced tumours that are rejected by non-irradiated syngeneic recipients (Fisher & Kripke, 1977; Fisher & Kripke, 2002). A photo-reactivating enzyme that is activated by visible light and repairs UV-induced CPD in DNA is present in marsupials, such as the opossum. UVB irradiation of the dorsal skin prevented these animals from developing a contact-hypersensitivity (CHS) response to dinitrofluorobenzene (DNFB). This effect was largely abolished when photo-reactivating light was given before the challenge with DNFB, which demonstrates the role of the pyrimidine dimer in this process (Applegate et al., 1989).

Exposure to UV induced apoptosis (TE#13) in human HaCaT keratinocytes. Conditioned medium collected 12 hours after UV exposure induced apoptosis in non-irradiated cells, and this effect increased progressively when conditioned medium collected 24 or 72 hours after UV exposure was

used (Banerjee et al., 2005). Exposure to UV of different human melanoma cell lines initiated progressive cell death associated with pronounced apoptosis, with UVA having a greater effect than UVB. Microsatellite instability was higher after UVB than after UVA (Hussein et al., 2005). While CPDs are the most important apoptosis-inducing UV-associated lesions in repair-proficient cells, recent data indicate that (6–4)-photoproducts act as a signal for apoptosis in human fibroblasts deficient in DNA repair (Batista et al., 2009). The receptor tyrosine kinase EPHA2 is an essential mediator in UV-induced apoptosis (Zhang et al., 2008).

UV can cause genomic instability (TE#16). UVA and UVB radiation induced persistent genomic instability in human cells in vitro (Phillipson et al., 2002; Hussein et al., 2005). UV radiation can also induce changes in vascularization (TE#19) in intrinsically aged and photo-aged human skin (Chung & Eun, 2007).

UVA can induce site-specific DNA-damage in telomere sequences (TE#20) in human fibroblasts and HL-60 leukaemia cells in vitro. A photo-excited endogenous photosensitizer was shown to oxidize the central guanine of 5'-GGG-3' in the telomere sequence to produce 8-oxodG, probably through an electron-transfer reaction. This site-specific damage may participate in the increase in the rate of telomere shortening (Oikawa et al., 2001b).

A bystander effect is defined as the induction of damage in non-irradiated cells by irradiated cells. UV radiation induced bystander signalling (TE#22) in human HaCaT keratinocytes and MRC5 fibroblasts in vitro (Banerjee et al., 2005; Whiteside & McMillan, 2009) and in V79 Chinese hamster fibroblasts in vitro (Dahle et al., 2005).

Repeated in-vitro exposures to UVA induced malignant transformation (TE#23) of human HaCaT cells, with acquired resistance to apoptosis induced not only by UVA but also by UVB, arsenite, and various other chemicals. Increased protein kinase B signalling and decreased expression of the tumour-suppressor PTEN may contribute to this malignant transformation (He et al., 2006). Multiple doses of combined UVA+UVB induced malignant transformation (TE#23) of human HaCaT keratinocytes (Gupta et al., 2006; Han et al., 2015).

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In vivo, sun-exposed skin of three whale species showed breaks and other lesions in mitochondrial DNA (Bowman et al., 2013). DNA breakage (measured by use of the comet assay) (TE#1) also appeared in peripheral lymphocytes of rats exposed to natural sunlight (Rodrigues-Junior et al., 2012). Increased frequencies of micronucleated erythrocytes (TE#4) were found in newborns of rat dams exposed to UVA during pregnancy (Zúñiga-González et al., 2015). The role of microRNAs (TE#6) in the dermal response to UV radiation has recently been reviewed (Syed et al., 2013; Syed et al., 2015). Mutations in the promoter of the telomerase reverse transcriptase (TERT) gene (TE#20) are common in melanoma, basal cell carcinoma and squamous cell carcinoma (Horn et al., 2013; Huang et al., 2013; Scott et al., 2014).

Tobacco Smoking (IARC, 2012e)

Tobacco smoke is a genotoxic and mutagenic mixture of thousands of chemicals (Hecht 1999; Hecht 2003; DeMarini 2004), some of which form adducts with DNA (TE#1) (Bartsch et al., 1993; Hang, 2010). In a pooled analysis of three prospective studies, an association was found between DNA-adduct levels and lung cancer risk, which was more obvious in current smokers. Likewise, in a meta-analysis of nine case–control studies, a significant association was found between lung or bladder cancer and the levels of bulky DNA adducts in current smokers (Veglia et al., 2008). Adducts have also been detected in animals exposed in vivo – whole-body or nose-only – to tobacco smoke (Bond et al., 1989; Gairola et al., 1991; Husgafvel-Pursiainen 2004). Other types of tobacco smoke-induced DNA damage included strand breaks (Nakayama et al., 1985; Holz et al., 1993) and oxidative lesions (TE#2), which have been found in a variety of tissues, including sperm, in smokers (DeMarini 2004) and in animals exposed in vivo (Husgafvel-Pursiainen 2004).

Smokers were shown to have significantly higher levels of sister chromatid exchange (SCE) (TE#1) in peripheral lymphocytes than non-smokers (Lambert et al., 1982; Perera et al., 1987; Sardaş et al., 1991). In some studies SCE formation in animals in vivo was reported, e.g. in bone-marrow cells of exposed mice (Benedict et al., 1984) and in fetal liver cells of mice exposed transplacentally (Karube et al., 1989), but in other reports SCE levels were not increased.

Tobacco smoke induces oxidative stress (TE#2) which results in oxidative damage to DNA and chronic inflammation (TE#12). This was supported by results of studies in humans in vivo or in human cells in vitro (Faux et al., 2009; Yanbaeva et al., 2007; Milara & Cortijo 2012), in laboratory experiments (Bhalla et al., 2009) and in animals in vivo (Verschuere et al., 2012).

Adducts between haemoglobin and different components of tobacco smoke (TE#3) were detected in the blood of smokers in a number of studies (Törnqvist et al., 1986; Bryant et al., 1987; Atawodi et al., 1998; von Stedingk et al., 2011). Protein adducts were also found in human alveolar basal epithelial A549 adenocarcinoma cells exposed in vitro to cigarette smoke (Rainey et al., 2009).

Tobacco smoke and several of its components cause cytogenetic damage (TE#4). Increased frequencies of micronuclei (Larramendy & Knuutila, 1991; Piyathilake et al., 1995) and chromosomal aberrations (CA) (Littlefield & Joiner 1986) were associated with tobacco smoking and with smokeless tobacco use ('chewing') in humans (Husgafvel-Pursiainen 2004). Buccal cells from smokers and 'chewers' display many of the changes associated with these two types of tobacco consumption (Proia et al., 2006). Cigarette-smoke condensate induced cytogenetic effects in vitro, in human diploid 2BS cells (Gu 1990), in human diploid GM03349B fibroblasts (Luo et al., 2004), and in animal cells and bacteria (DeMarini et al., 2008). SCE and CA were increased in human lymphocytes treated in vitro with the tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Salama et al., 1999).

In lung adenocarcinomas from 92 smokers and 14 non-smokers, mutations (TE#5) in the oncogene *K-RAS* were detected in 40 tumours, all from smokers (Ahrendt et al., 2001). Mutations in TP53 were found in smoking-associated cancers in smokers (Husgafvel-Pursiainen et al., 1995; Pfeifer et al., 2002). Activated K-Ras genes were detected in mouse lung tumours induced by NNK (Reynolds & Anderson 1991). Mutations at the HPRT locus were found in peripheral T-lymphocytes of smokers (Hackman et al., 2000). Both active and passive exposure to tobacco smoke in utero resulted in increased mutation at the HPRT locus in the fetus (Grant 2005).

Tobacco smoke also operates via epigenetic mechanisms (TE#6). Lung cells from smokers were shown to carry promoter methylations of critical genes such as *CDKN2A* (encoding protein p16) and *FHIT* (fragile histidine triad) (Belinsky et al., 2002; Kim et al., 2004; Belinsky, 2005; Bhutani et al., 2008). Studies of human cells exposed to cigarette-smoke condensate in vitro also reported histone alterations, genomic hypomethylation and local DNA hypermethylation (Liu et al., 2010). Epigenetic alterations in tumour suppressor genes, particularly methylation of CDKN2A, may be an important mechanism for K-RAS-related tumorigenesis, but one that is rarely involved in the EGFR-related pathway (Toyooka et al., 2006). Epigenetic transcriptional silencing (TE#6) of genes via CpG-island hypermethylation has become known as a critical component in the initiation and progression of lung cancer (Belinsky 2005). In the rat, nearly all adenocarcinomas induced by the tobacco-specific carcinogen NNK were hypermethylated at the *CDKN2A* promoter (Belinsky et al., 1998). In human squamous cell carcinomas (SCC), the p16-encoding gene *CDKN2A* was methylated in 75% of adjacent carcinoma-*in-situ* lesions. Moreover, in premalignant lesions obtained from persons without SCC, the methylation frequency of this gene increased from 17% in basal cell hyperplasia, to 24% in squamous cell metaplasia, to 50% in carcinoma in situ (Belinsky et al., 1998).

Changes in protein expression (TE#7) were observed in bronchial brush specimens from heavy smokers, where NNK enhanced the synthesis of the protein survivin in epithelial cells (Jin et al., 2008). Similar changes were reported for the Akt protein in human airway epithelial cells exposed to NNK in

vitro (West et al., 2003), and for the Fhit protein in rodents exposed to environmental cigarette smoke in vivo (D'Agostini et al., 2006).

Key pathways altered in human lung adenocarcinoma (TE#8) correlated with smoking status (Ding et al., 2008). Analysis of transcriptional profiles resulting from exposure to complex mixtures such as cigarette smoke demonstrated changes in transcription of numerous genes in human cells in vitro (Sen et al., 2007).

The genetic constitution of female smokers, in particular the *N*-acetyltransferase 2 (NAT2) slow-acetylation genotype (TE#10) enhances their risk for smoking-associated breast cancer (Ambrosone et al., 2008), but this genotype does not clearly influence the bacterial mutagenicity of smokers' urine (Hirvonen et al., 1994; Pavanello et al., 2002). In-vitro genotoxicity studies with human cells revealed evidence of genotype-carcinogen interactions, e.g. those associated with glutathione S-transferases M1 and T1 (Norppa 2003).

Tobacco smoke has been shown to affect the immune system, in particular early immune function (TE#11). Total leukocyte counts, most prominently segmented neutrophils, lymphocytes, and myeloid precursor dendritic cells, were reduced in neonates of smoking mothers compared with controls. These effects reflect an impact of maternal smoking on the developing fetal immune system (Pachlopnik Schmid et al., 2007). In human THP-1 monocytes and lung macrophages, exposure to cigarette smoke delayed the production of innate cytokines IL-1beta and IL-6, and reduced glutathione levels. These effects were associated with a reduction in NF-kappaB pathway activation (Birrell et al., 2008). The effects of tobacco smoking on early immune function through alterations in cytokine production in the feto-placental unit have been detected ex vivo in cord blood. Newborns of smoking mothers had altered signalling through Toll-like receptors, which are essential for innate microbial responses. These effects may play a part in the greater predisposition to infection among smoke-exposed infants (Prescott 2008). Chronic exposure of the bronchial epithelium to cigarette smoke caused increased production of metalloproteinases (MMP) by macrophages and of proteolytic enzymes by neutrophils (Domagala-Kulawik 2008). Chronic inhalation of cigarette smoke in rats preferentially inhibited the plaque-forming cell response of lung-associated lymph nodes to the T-cell dependent antigen SRBC (sheep red blood cells), compared with anatomically distant lymph nodes; this reduction of the antibody response primarily involved the B-cell function (Sopori et al., 1989). Chronic exposure to cigarette smoke inhibited surface immunoglobulin-mediated responses in B-cells of rats (Savage et al., 1991).

Exposure of pregnant B6C3F1 mice to inhaled mainstream cigarette smoke throughout gestation caused a significant increase in circulating white blood cell and lymphocyte counts in the offspring for up to 2.5 months after birth, a decrease in mitogen-stimulated T-lymphocyte proliferation in 3-wk-old offspring, and an increase in mixed lymphocyte response in 5-wk-old male pups, compared with corresponding effects in sex-matched, air-exposed controls (Ng & Zelikoff 2008). Exposure of ovalbumin-sensitized mice to mainstream cigarette smoke suppressed the allergic airway response and reduced eosinophilia, tissue inflammation, goblet cell metaplasia, concentrations of IL-4 and IL-5 in broncho-alveolar lavage (BAL) fluid, and ovalbumin-specific antibodies. These effects are associated with a loss of antigen-specific proliferation and cytokine production by T-cells (Thatcher et al., 2008).

Chronic inflammation (TE#12) is a known cancer promoter that is induced by smoking as reported in studies in humans in vivo and in human cells or organ explants in vitro (van der Vaart et al., 2004; Smith et al., 2006; Walser et al., 2008; Zhou et al., 2009).

Metals found in tobacco smoke, which may have a role in lung carcinogenesis, interfere with apoptosis (TE#13) as was reported in studies in humans in vivo (Stavrides 2006). In-vitro treatment of human airway epithelial cells with nicotine or NNK attenuated apoptosis and partially induced a transformed phenotype, with loss of contact inhibition and independence from exogenous growth factors (West et al., 2003).

Both active smoking and exposure to second-hand smoke are irritants (TE#14) that increase the risk of chronic rhinitis (Higgins & Reh, 2012), and may cause bronchial irritation leading to asthma. In-

utero exposure to maternal smoking may be independently responsible for early-onset asthma (Jindal & Gupta 2004).

Components of cigarette smoke have effects on the cell cycle (TE#15). In a study of 188 primary human lung adenocarcinomas, somatic mutations were detected for several tumour-suppressor genes involved in critical pathways of cell proliferation, e.g. the ATM gene, which encodes a cell-cycle checkpoint kinase that functions as a regulator of TP53 (Ding et al., 2008). Cigarette-smoke extract was shown to induce G1 cell-cycle arrest in endothelial cells in vitro (Henderson et al., 2008). In murine or human lung epithelial cells, DNA synthesis was inhibited after exposure to benzo(a)pyrene (B(a)P), an important combustion product in tobacco smoke, along with activation of the DNA-damage checkpoint. Co-treatment with nicotine compromised the growth restriction and induced upregulation of cyclins D and A. Nicotine is thus able to override the DNA-damage checkpoint activated by a tobacco-related carcinogen (Nishioka et al., 2011).

The tobacco-smoke constituent 4-aminobiphenyl induced chromosomal instability (TE#16) in human cancer cells in vitro (Saletta et al., 2007). Similarly, cigarette-smoke condensate induced genetic instability in human airway epithelial cells (Hays et al., 2008). In vivo, short-term exposure to mainstream or side-stream tobacco smoke – STS, the main component of second-hand smoke – induced mutations (TE#5) at an expanded simple tandem-repeat locus (Ms6-hm) in mouse sperm (Marchetti et al., 2011). Cigarette smoke induced telomere dysfunction and chromosomal instability in mouse embryos in vitro (Huang et al., 2010). Lung adenocarcinomas obtained from never smokers and smokers harbour different regions of genetic alteration and display different levels of genomic instability. Microsatellite instability has been found in DNA samples from colon cancer of smokers (Slattery et al., 2000).

Receptor-mediated effects (TE#17) of various tobacco products were reported in studies with human placental tissue after maternal smoking (Wang et al., 1988), in human epidermal melanocytes exposed in vitro to tobacco-smoke extract (Nakamura et al., 2013), in human adenocarcinoma cells exposed in vitro to NNK (Schuller et al., 1999), and in mouse hepatoma cells exposed in vitro to cigarette-smoke condensate (Meek & Finch, 1999; Dertinger et al., 1998).

Cigarette-smoke condensate and NNK induced malignant transformation of human cells (TE#23) in vitro (Narayan et al., 2004; Zhou et al., 2003).

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Protein adducts (TE#3) were found in guinea-pigs exposed to cigarette smoke in vivo, and in serum of human smokers (Ghosh et al., 2012). Studies of human cells exposed to cigarette-smoke condensate in vitro revealed (TE#6) histone alterations, hypermethylation (Word et al., 2013), histone acetylation (Sundar et al., 2014) and repression of microRNAs (Xi et al., 2013). Cigarette-smoke condensate (CSC) caused malignant transformation of human MCF-10A breast epithelial cells (TE#23). This transforming capacity was linked to the presence of cadmium in the CSC, since treatment of the cells with CdCl2 had comparable transforming effects (Mohapatra et al., 2014).

TCDD (IARC, 2012f)

Most, if not all the effects of TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin, 2,3,7,8-TCDD, dioxin) are related to its binding to and activation of the aryl hydrocarbon receptor (AhR).

TCDD is not directly genotoxic. It induced DNA strand breaks (TE#1) as a result of oxidative stress (TE#2) in human breast carcinoma cell lines (Lin et al., 2007) and it modulated DNA strand-break induction by estrogen in these cells (Lin et al., 2008). TCDD caused single-strand breaks in liver DNA of rats treated in vivo, in conjunction with lipid peroxidation (Wahba et al., 1988). These effects may be related to a TCDD-induced increase in the bioavailability of iron (Wahba et al., 1989). Formation of

oxidative DNA damage upon treatment with TCDD was more pronounced in intact rats compared with ovariectomized rats, possibly as a result of enhanced metabolic activation of estrogens to catechols by TCDD-induced enzymes. Expression of CYP1B1, an enzyme with estrogen hydroxylase activity, was induced by TCDD (Tritscher et al., 1996; Wyde et al., 2001). Sustained oxidative stress was observed in TCDD-treated mice (Shertzer et al., 1998). In the [32P]-postlabeling assay, TCDD-specific DNA adducts were not detected in the liver of treated male or female rats; however, in this assay TCDD caused a dose-dependent decrease in several I-compounds in the liver of female, but not male rats; this effect was not seen in the kidney. These findings correlate with the organ/sex specificity of TCDD as a carcinogen. Experiments with differently substituted dibenzodioxins showed that their effects on hepatic I-compounds correlated with their corresponding structure–Ah receptor binding (Randerath et al., 1988; Randerath et al., 1990).

TCDD is clastogenic in various test systems (TE#4). It induced micronuclei in lymphocytes of two TCDD-intoxicated subjects (Valic et al., 2004), in cultured human lymphocytes (Nagayama et al., 1993), in primary rat hepatocytes in vitro (Turkez et al., 2012a), and in rats exposed in vivo (Türkez et al., 2012b). Increased frequencies of chromosomal aberrations were found in fetal tissues in a group of TCDD-exposed pregnancies after the Seveso accident (Tenchini et al., 1983). Increased frequencies of chromosome aberrations and sister chromatid exchange (SCE) were measured in sheep exposed to high levels of TCDD during pasturage (Perucatti et al., 2006).

TCDD induced intra-chromosomal recombination (TE#4) in mice in vivo (Schiestl et al., 1997). TCDD was mutagenic (TE#5) in the mouse lymphoma assay (Rogers et al., 1982) and in various other tests for mutagenicity (Escherichia coli, yeast), but did not give a mutagenic response in Salmonella typhimurium (Giri 1986). TCDD suppressed the expression of the checkpoint protein Mad2, which has an important role in accurate chromosome segregation in mitotic cells. This effect was seen also seen in AhR-deficient (-/-) mouse embryonic fibroblasts (MEF). TCDD thus increased chromosomal instability (TE#16) through the suppression of Mad2 expression through an AhR-independent pathway (Oikawa et al., 2001a).

TCDD induced changes gene expression (TE#7) in human and animal cells in vitro, and in animals in vivo (Kim et al. 2009b; Dere et al., 2006). In a comparative inter-species analysis of the effects of TCDD on hepatic gene expression in rats and mice, responses conserved between species were associated with xenobiotic and chemical stress, and with alterations in amino acid and lipid metabolism (Boverhof et al., 2006). A two-fold or greater downregulation of abour 60 hepatic genes was found in rats after subchronic exposure (13 weeks) to TCDD (Ovando et al., 2006).

TCDD is a strong inducer of several cytochrome-associated enzymes (TE#7), in particular CYP1A1 (Denison & Whitlock 1995; Micka et al., 1997; Whitlock 1999) and CYP1B1 (Tritscher et al., 1996; Wyde et al., 2001).

TCDD induces epigenetic effects (TE#6) (not discussed in Monograph Vol. 100F; see review by Baccarelli & Bollati 2009). Analysis of T-cells in mesenteric lymph nodes during chemically induced acute colitis in mice revealed increased methylation of CpG islands in the immune regulator Foxp3 and demethylation of IL-17 promoters. Both effects were reversed upon treatment with TCDD: the activation of AhR by TCDD thus led to demethylation or methylation of regulatory genes (Singh et al., 2011). Changes in DNA methylation and gene expression were observed in splenocytes of mice upon TCDD-induced suppression of the lipopolysaccharide-stimulated IgM response (McClure et al., 2011). Acetylation of histones H3 and H4 and tri-methylation of histone H3 were detected at the promoter regions of CYP1A1 and CYP1B1 in human MCF-7 breast cancer cells and in human HepG2 hepatic cancer cells exposed to TCDD (Beedanagari et al., 2010). A single intraperitoneal dose of TCDD dysregulated the expression of the microRNAs miR101a and miR122 in mice (Yoshioka et al., 2011). In mouse embryo fibroblasts exposed to TCDD in vitro, miR101a was one of five prominently upregulated miRNAs (Huumonen et al., 2014).

In female rats initiated with diethyl-nitrosamine and subsequently treated with TCDD, persistent liver-cell proliferation (TE#15) and growth of enzyme-altered foci were seen after chronic exposure during 30 weeks followed by cessation of treatment (Tritscher et al., 1995). TCDD induced expression of AhR-responsive genes in the pituitary of mice treated in vivo (Huang et al., 2002). TCDD increased CYP1A1 mRNA expression in the retina of mice treated in vivo. It also promoted the expression of vascular endothelial growth factor-A in the retina and the retinal pigment epithelium of these mice, as well as in human retinal pigment epithelial cells (Takeuchi et al., 2009). Inherent differences were observed in TCDD-mediated gene-expression responses between mouse hepatoma cells in vitro and in hepatic tissue from TCDD-treated mice. Induction of genes involved in xenobiotic metabolism was noted in both systems. Responses associated with cell-cycle progression and cell proliferation were only seen in vitro, whereas those associated with lipid metabolism and immune effects were observed only in vivo (Dere et al., 2006). In human CD34+ cells, TCDD modulated numerous transcripts involved in cell cycle or cell proliferation, immune response, signal transduction, ion-channel activity or calcium binding, tissue development and differentiation, and female or male fertility (Fracchiolla et al., 2011).

TCDD interferes with different cell-signalling pathways (TE#8). Alteration of cell signalling by TCDD has been observed in animals in vivo and in animal cells in vitro. TCDD activated the MAPK pathway via an AhR-independent mechanism in RAW 264.7 murine macrophages (Park et al., 2005). TCDD caused concentration-dependent anatomical rearrangements in the shape of the prosencephalic artery in zebrafish larvae through activation of Ahr2/Arnt1 pathway (Teraoka et al., 2010).

A number of epidemiological studies among populations exposed to TCCD found no clear association between exposure and altered immunological status (IARC, 1997), and immune effects of TCDD are not mentioned in Monograph Volume 100. However, TCDD has immunosuppressive and immunotoxic properties (TE#11) (Vineis & Zahm 1988; Kerkvliet 2002). In T-cells isolated from a small number of TCDD-exposed industrial workers, the capacity to proliferate upon interleukin-2 stimulation was significantly diminished, with TCDD showing a long-term immunosuppressive effect on T-helper cell function (Tonn et al., 1996). In human CD34+ cells, TCDD modulated numerous transcripts involved in cell cycle or cell proliferation, immune response, signal transduction, ion-channel activity or calcium binding, tissue development and differentiation, and female or male fertility (Fracchiolla et al., 2011). Further evidence for effects of TCDD on the immune system comes from animal studies. A single subcutaneous injection of TCDD caused a significant reduction in the number of total peripheral lymphocytes in marmosets (Neubert et al., 1993). Crossing the placenta during gestation, TCDD produced fetal thymic atrophy, inhibited thymocyte maturation and reduced expression of thymic MHC class II molecules in mice (Holladay 1999). TCDD dose-dependently reduced the number of lipopolysaccharide-induced IgM antibody-forming cells in mice; this effect was correlated with a lower frequency of CD19+/CD138+ cells (North et al., 2009). Activation of the AhR by TCDD in mice dosed orally during an acute graft-versus-host response induced a population of alloreactive donor CD4+/CD25+ regulatory T (Treg)-like cells that had potent suppressive activity in vitro (Funatake et al., 2005). TCDD had a direct effect on cultured mouse lymphocytes resulting in the selective inhibition of the differentiation of B-cells into antibody-secreting cells (Tucker et al. 1986). Direct AhR-dependent effects of TCDD in both CD4+ and CD8+ T-cell subsets in the mouse contributed to the complete suppression of the cytotoxic T lymphocyte response, indicating that expression of the AhR is not required for the development of an immune response, but is required for TCDD-induced immune suppression (Kerkvliet et al., 2002).

TCDD induced a switch from proliferation (TE#15) to terminal differentiation in primary cultures of human keratinocytes (Berkers et al., 1995). The 17-beta-estradiol-stimulated cell proliferation and increase in cellular DNA content of estrogen-responsive MCF-7 human breast-cancer cells were both inhibited by TCDD. This effect was not seen in MDA-MB-231 breast-cancer cells, which are non-responsive to estrogen (Biegel & Safe 1990). Positive dose–response relationships were seen for the effects of TCDD on cell proliferation and growth of altered hepatic foci in female rats exposed in vivo

(Maronpot et al., 1993). The dose–response was different from that observed for the effects of TCDD on CYP450 gene expression in the same test system (Tritscher et al., 1992).

TCDD inhibited apoptosis (TE#13) in human bronchial epithelial cells in vitro (Chen et al., 2014). TCDD stimulated proliferation of human SaOS-2 osteogenic sarcoma cells, increased the synthesis of alkaline phosphatase, and reduced apoptosis in a dose-dependent manner (Guo et al., 2008). TCDD caused an early increase in intracellular calcium and subsequent apoptosis in human L-MAT lymphoblastic T-cells, which do not express the AhR. An antagonist of calcium-dependent calmodulin blocked this effect, which suggests that calcium/calmodulin signals play an important part in the induction of apoptosis in L-MAT cells by TCDD (Kobayashi et al., 2009). In SHSY5Y human neuroblastoma cells in vitro, TCDD induced loss of viability, which was linked to increased caspase-3 activity, PARP-1 fragmentation, DNA laddering, nuclear fragmentation and hypo-diploid (apoptotic) DNA content (Morales-Hernández et al., 2012). Male rats treated orally with TCDD showed functional and structural damages as well as apoptosis in spermatogenic cells. These effects were associated with lipid peroxidation (Sönmez et al., 2011). In rabbit chondrocytes in vitro, TCDD caused an increase of apoptotic effects in a dose-dependent manner. This effect was blocked by inhibitors of reactive oxygen species (ROS) or nitric oxide (NO), suggesting that the increase in apoptosis was mediated via ROS/NO-dependent pathways (Yang & Lee 2010). In primary rat hepatocytes in vitro, TCDD inhibited UVC-induced apoptosis; this effect was dependent on AhR-activation (Chopra et al., 2010). TCDD induced apoptotic cell death with nuclear fragmentation and DNA laddering in cerebellar granule cells (CGC) from AhR+/+ but not AhR−/− mice (Sánchez-Martin et al., 2011). TCDD significantly induced apoptosis in primary cortical neurons of the rat and in differentiated rat PC12 pheochromocytoma cells. The activation of MAPK signalling pathways was associated with this TCDD-mediated neuronal apoptosis (Xu et al., 2013c).

TCDD induces a wide variety of AhR-mediated effects (TE#17). AhR activation by TCDD enhanced the invasiveness of human gastric cancer cells, likely through a c-Jun-dependent induction of matrix metalloproteinase-9 (Peng et al., 2009). Exposure to TCDD significantly decreased the plasma insulin concentration after a glucose challenge in AhR+/+ mice but not in AhR−/− mice (Kurita et al., 2009). TCDD increased the serum glucose levels in AhR-sensitive C57BL/6J mice, but not in the less sensitive DBA/2J mice. The expression of intestinal mRNAs encoding sodium-glucose co-transporter 1 (SGLT1) and glucose transporter type 2 were thus increased only in the C57BL/6J mice by TCDD (Ishida et al., 2005). In mouse hepatoma Hepa-1c1c7 cells, TCDD increased mRNA expression of the gene encoding phospholipase A(2)alpha and enhanced the activity of the corresponding enzyme, while these effects were not observed in AhR-defective c12 cells (Kinehara et al., 2009). TCDD induced AhR-mediated apoptosis in the avian DT40 pre-B-cell line through activation of caspases 9 and 3 (Puebla-Osorio et al., 2004). TCDD induced plasminogen activator inhibitor-1 through an AhR-mediated pathway in mouse hepatoma cells (Son & Rozman, 2002). Short-term in-vitro exposure of MRC-7 human breast cancer cells to TCDD resulted in the suppression of estrogen receptor-alpha protein expression (Marquez-Bravo & Gierthy 2008).

TCDD interferes with endogenous hormones (TE#18). TCDD induced enzymes that increased metabolism of endogenous estrogens to catechols in rats (Tritscher et al., 1996; Wyde et al., 2001). TCDD induced estrogenic action or inhibited estrogen-induced effects in various tissues because of cross-talk between the estrogen receptor and AhR (Ohtake et al., 2008). TCDD affected the expression levels of a series of estrogen-responsive genes in MCF-7 human breast carcinoma cells and RL95–2 human endometrial carcinoma cells (Tanaka et al., 2007).

TCDD promoted the transformation (TE#23) of C3H/10T1/2 cells pre-treated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) (Abernethy et al., 1985). Dysregulation of growth regulatory factors such as PAI-2, TGF-beta1 and TNF-alpha were suggested to be involved in TCDD-induced transformation of human cells (Yang et al., 1999). TCDD immortalized normal human keratinocytes in

an AhR-dependent process, presumably by suppressing two key initiators of senescence, p16INK4a and p53. This suppression was accompanied by promoter methylation (Ray & Swanson, 2004).

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TCDD induces effects on cell-signalling pathways (TE#8). TCDD suppressed the attachment of spheroids onto human endometrial epithelial cells by inducing CYP1A1 expression and by modulating the Wnt-signalling pathway (Tsang et al., 2012). In human bronchial epithelial cells, TCDD inhibited the apoptotic effect of staurosporine, at least in part, through activation of the Akt and ERK1/2 signalling pathways (Chen et al., 2014). In the rat brain cortex and in rat PC12 neuronal cells, TCDD caused a significant downregulation of β-catenin and phosphoglycogen-synthase kinase-3β (pSer9-GSK-3β), which are elements in the Wnt/β-catenin signalling pathway (Xu et al., 2013d). TCDD stimulated cell proliferation in the cortex of the rat brain by affecting the Akt/GSK-3β/cyclin D1 signalling pathway (Xu et al., 2014b).

TCDD causes Epigenetic effects (TE#6). TCDD induced epigenetic transgenerational inheritance of adult-onset disease and epi-mutations in sperm. When gestating female rats (F0) were exposed to TCDD and F1–F3 generations were obtained in the absence of exposure, TCDD was found to promote early-onset female puberty, to affect spermatogenic cell apoptosis, and to decrease the pool size of ovarian primordial follicles. Differential DNA methylation regions were identified in the sperm of all males in the F1–F3 generations (Manikkam et al., 2012a; Manikkam et al., 2012b).

In human glioma cells in vitro, TCDD stimulated transcription and activity of CYP19 (aromatase) (TE#7), which is responsible for estrogen synthesis. In glial cells of the brain, estrogen maintains normal brain function, ranging from neurotransmission to synapse formation. Therefore, this effect of TCDD may perturb hormonal balance in the brain (Tan et al., 2013). TCDD induced genomic instability (TE#16) in mouse embryonic fibroblasts (Korkalainen et al., 2012).

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