

Annex 5 – Glossary of Terms

3R's principle: The 3Rs stand for Replacement, Reduction, Refinement. This is a strategy that is intended to reduce the number of animals used in experiments and to reduce animal experimentation overall; it also aims to mitigate the suffering and distress caused to the animals.

a priori: The formulation of an hypothesis based on theoretical considerations before undertaking an investigation or experiment.

Absolute risk (AR): is the probability or chance of an event. It is usually used for the number of events (such as a disease) that occurred in a group, divided by the number of people in that group.

Absorption (biological): Process of active or passive transport of a substance into an organism, in humans this is usually through the lungs, gastrointestinal tract or skin.

Acceptable daily intake (ADI): Estimate of the amount of a substance in food or drink, expressed on a bodyweight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk.

Acceptable risk: Probability of suffering disease or injury which is considered to be sufficiently small to be societally acceptable.

Acute: Short term, in relation to exposure or effect.

Acute reference dose (ARfD): Estimate of the amount of a substance in food or drink, expressed on a body weight basis that can be ingested in a period of 24 hours or less without appreciable health risk.

Acute toxicity: Adverse effects that occur over a short period of time (up to 14 days) immediately following a single exposure.

Adaptive response: The process whereby a cell or organism responds to a xenobiotic so that the cell or organism will survive in the new environment that contains the xenobiotic without impairment of function.

Adduct: A chemical grouping which is covalently bound (see covalent binding) to a large molecule such as DNA (qv) or protein.

Adductome: The totality of the adduct profile, usually to DNA, in an individual.

Adenoma: A benign neoplasm arising from a gland forming epithelial tissue such as colon, stomach or respiratory tract.

Adverse Outcome Pathway (AOP): A sequence of key events linking a molecular initiating event (MIE) to an adverse outcome through different levels of biological organisation. AOPs span multiple layers of biological organisation.

Adverse response: Change in morphology, physiology, biochemistry, growth, development or lifespan of an organism or its progeny which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences.

Aetiology: study of causation or origination.

Aggregate exposure: exposure to one chemical by all routes from all sources.

Ah receptor: The Ah (Aromatic hydrocarbon) receptor protein is a member of a group of regulatory sensor molecules. The identity of the natural endogenous chemicals which regulate the Ah receptor is unknown. Binding to the Ah receptor is an integral part of the toxicological mechanism of a range of chemicals, such as chlorinated dibenzodioxins and polychlorinated biphenyls.

Alkylating agents: Chemicals which leave an alkyl group covalently bound to biologically important molecules such as proteins and nucleic acids (see adduct). Many alkylating agents are mutagenic, carcinogenic and immunosuppressive.

Allele: Alternative form of a gene within the population.

Allergen: Substance capable of stimulating an allergic reaction.

Allergy: The adverse health effects that may result from the stimulation of a specific immune response.

Allergic reaction: an adverse reaction elicited by exposure to a previously sensitised individual to the relevant antigen.

Ames test: Also known as the bacterial reverse mutation assay. In vitro assay for bacterial gene mutations using strains of *Salmonella typhimurium* and *Escherichia coli*.

Androgen: The generic term for any natural or synthetic compound that can interact with and activate the androgen receptor. In mammals, androgens (for example, androstenedione and testosterone) are synthesised by the adrenal glands and the testes and promote development and maintenance of male secondary sexual characteristics.

Aneugen/aneugenic: (An agent) Inducing aneuploidy.

Aneuploidy: The circumstances in which the total number of chromosomes within a cell is not an exact multiple of the normal haploid (see 'polyploidy') number. Chromosomes may be lost or gained during cell division.

Apoptosis: A form of programmed, active cell death resulting in fragmentation of the cell into membrane-bound fragments (apoptotic bodies). These are usually rapidly removed in vivo by engulfment by phagocytic cells. Apoptosis occurs normally during development but can be triggered abnormally by toxic stimuli.

As low as is reasonably achievable/ As low as is reasonably practicable (ALARA/ALARP): A risk management approach under which exposure to a substance or mixture is reduced to the lowest level that it is deemed to be reasonably achievable or practicable in particular circumstances or by available technological solutions.

Base pair (bp): Two complementary nucleotide bases in DNA joined together by hydrogen bonds.

Benchmark dose (BMD) modelling: An alternative quantitative approach to dose-response assessment using more of the data than the NOAEL process. This approach utilises mathematical models to fit all available data points and uses the best fitting model to interpolate an estimate of the dose (benchmark dose) that corresponds to a particular level of response (a benchmark response). A measure of uncertainty is also calculated, and the lower confidence limit on the benchmark dose is called the BMDL. The BMDL accounts for the uncertainty in the estimate of the dose-response that is due to characteristics of the experimental design such as sample size and biological variability. The BMDL can be used as the point of departure (see POD) for derivation of a health-based guidance value or a margin of exposure.

Benign tumour: Tumours showing a close morphological resemblance to their tissue of origin, growing in a slow expansile fashion and with a circumscribed form, usually encapsulated masses. They may stop growing and they may regress. Benign tumours do not infiltrate through local tissues, and they do not metastasise. They are rarely fatal.

Bias: An interference which at any stage of an investigation tends to produce results that depart systematically from the true values (to be distinguished from random error). The term does not necessarily carry an imputation of prejudice or any other subjective factor such as the experimenter's desire for a particular outcome.

Bioavailability: A term referring to the proportion of a substance which reaches the systemic circulation unchanged after a particular route of administration.

Bioinformatics: The science of informatics as applied to biological research. Informatics is the management and analysis of data using advanced computing techniques. Bioinformatics is particularly important as an adjunct to -omics research, because of the large amount of complex data this research generates.

Biological relevance: an effect considered by expert judgement as important and meaningful for human, animal, plant or environmental health. It therefore implies a change that may alter how decisions for a specific problem are taken.

Biomarker: Observable change (not necessarily pathological) in an organism, related to a specific exposure, effect or susceptibility.

Biomarker of effect: A measurable biochemical, physiologic, behavioural, or other alteration in an organism that, depending on the magnitude, can be recognised as associated with an established or possible health impairment or disease.

Biomarker of exposure: a chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in the human body indicative of exposure.

Biomarker of susceptibility: An indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific chemical substance.

Biomonitoring (human): the direct measurement of people's integrated exposure to toxic substances by measuring the substances, their metabolites or a biochemical change in human specimens, such as blood or urine.

Biomonitoring equivalent: an estimated concentration or range of concentrations of an environmental chemical in humans which is consistent with existing health-based guidance values such as the TDI or RfD/RfC. BEs provide a way of interpreting biomonitoring data in the context of these values.

Body burden: Total amount of a chemical present in an organism at a given time.

Bradford Hill considerations: Sir Austin Bradford Hill established a set of 'principles' (not be taken as 'criteria') that may be used to assist in the interpretation of associations reported from epidemiological studies:

Strength – The stronger the association the more likely it is causal. The COC has previously noted that the relative risks of <3 need careful assessment for effects of bias or confounding.

Consistency – The association has been consistently identified by studies using different approaches and is also seen in different populations with exposure to the chemical under consideration.

Specificity – Limitation of the association to specific exposure groups or to specific types of disease increases likelihood that the association is causal.

Temporality – The association must demonstrate that exposure leads to disease. The relationship of time since first exposure, duration of exposure and time since last exposure are all important in assessing causality.

Biological gradient – If an association reveals a biological gradient or dose response curve, then this evidence is of particular importance in assessing causality.

Plausibility – Is there appropriate data to suggest a mechanism by which exposure could lead to concern? However, even if an observed association may be new to science or medicine it should not be dismissed.

Coherence – Cause and effect interpretation of data should not seriously conflict with generally known facts.

Experiment – Can the association be demonstrated experimentally? Evidence from experimental animals may assist in some cases. Evidence that removal of the exposure leads to a decrease in risk may be relevant.

Analogy – Have other closely related chemicals been associated with the disease?

Bronchial: Relating to the air passages conducting air from the trachea (windpipe) to the lungs.

Cancer: Synonym for a malignant neoplasm – that is, a tumour that grows progressively, invades local tissues and spreads to distant sites (see also tumour and metastasis).

Candidate gene: A gene that has been implicated in causing or contributing to the development of a particular disease.

Carcinogen: A causal agent that induces tumours. Carcinogens include external factors (chemicals, physical agents, viruses) and internal factors such as hormones. An important distinction can be drawn between **genotoxic** carcinogens which have been shown to damage DNA, and **nongenotoxic** carcinogens which act through other mechanisms. The activity of genotoxic carcinogens can often be predicted from their chemical structure - either of the parent compound or of active metabolites. Most chemical carcinogens exert their effects after prolonged exposure, show a dose-response relationship and tend to act on a limited range of susceptible target tissues. Carcinogens are sometimes species or sex-specific and the term should be qualified by the appropriate descriptive adjectives to aid clarity. Several different chemical and other carcinogens may interact, and constitutional factors (genetic susceptibility, hormonal status) may also contribute, emphasising the multifactorial nature of the carcinogenic process.

Carcinoma: Malignant tumour arising from epithelial cells lining, for example, the alimentary, respiratory and urogenital tracts and from epidermis, also from solid viscera such as the liver, pancreas, kidneys and some endocrine glands. (See also 'tumour').

Case-control study: (Synonyms - case comparison study, case referent study) A comparison is made of the proportion of cases who have been exposed to a particular hazard (e.g., a carcinogen) with the proportion of controls who have been exposed to the hazard.

Cell cycle (cell cycle arrest): The cell cycle is a series of events involving the growth, replication, and division of a eukaryotic cell. Cell cycle arrest: A regulatory process that halts progression through the cell cycle during one of the normal phases (G1, S, G2, M).

Cell transformation: The process by which a normal cell acquires the capacity for neoplastic growth. Complete transformation occurs in several stages both in vitro and in vivo. One step which has been identified in vitro is 'immortalisation' by which a cell acquires the ability to divide indefinitely in culture. Such cells do not have the capacity to form tumours in animals but can be induced to do so by extended passage in vitro, by treatment with chemicals, or by transfection with oncogene DNA.

The transformed phenotype so generated is usually, but not always, associated with the ability of the cells to grow in soft agar and to form tumours when transplanted into animals. It should be noted that each of these stages of transformation can involve multiple events which may or may not be genetic. The order in which these events take place, if they occur at all, in vivo is not known.

Cholinergic: A substance which is capable of producing, altering or releasing the neurotransmitter acetylcholine.

Chromosomal aberrations: Collective term of particular types of chromosome damage induced after exposure to exogenous chemical or physical agents which damage the DNA (see also aneugen, clastogen). Such numerical or structural chromosome changes tend to be those which are evident using light microscopy.

Chromosome: In simple prokaryotic organisms, such as bacteria and most viruses, the chromosome consists of a single circular molecule of DNA containing the entire genetic material of the cell. In eukaryotic cells, the chromosomes are thread-like structures, composed mainly of DNA and protein, which are present within the nuclei of every cell. They occur in pairs, the numbers varying from one to more than 100 per nucleus in different species. Normal somatic cells in humans have 23 pairs of chromosomes, each consisting of linear sequences of DNA which are known as genes.

Chronic effect: Consequence which develops slowly and has a long-lasting course (often but not always irreversible).

Chronic exposure: Continued exposures occurring over an extended period of time, or a significant fraction of the life-time of a human or test animal.

Clastogen: An agent that produces chromosome breaks and other structural aberrations such as translocations. Clastogens may be viruses or physical agents as well as chemicals. Clastogenic events play an important part in the development of some tumours (clastogenicity).

Clearance: Volume of blood or plasma, or mass of an organ, effectively cleared of a substance by elimination (metabolism and excretion) in a given time interval. Total clearance is the sum of the clearances for each eliminating organ or tissue.

Clone: A term which is applied to genes, cells, or entire organisms which are derived from - and are genetically identical to - a single common ancestor gene, cell, or organism, respectively. Cloning of genes and cells to create many copies in the laboratory is a common procedure essential for biomedical research.

Coding regions: those parts of the DNA that contain the information needed to form proteins. Other parts of the DNA may have non-coding functions (e.g., start-stop, pointing or timer functions) or as yet unresolved functions or maybe even 'noise'.

Codon: a set of three nucleotide bases in a DNA or RNA sequence, which together code for a specific amino acid.

Cohort: A defined population that continues to exist through a period of time, e.g., a group of individuals who had a specific occupation.

Cohort study: (Synonyms - follow-up, longitudinal study) The study of a group of people defined at a particular point in time (the cohort), who have particular characteristics in common, such as a particular exposure. They are then observed over a period of time for the occurrence of disease. The rate at which the disease develops in the cohort is compared with the rate in a comparison population, in which the characteristics (e.g., exposure) are absent.

Combined exposure: exposure to multiple chemicals by a single or multiple routes at the same or different times.

Comet assay: A genotoxicity assay in which DNA strand breaks in an individual cell are measured using single-cell gel electrophoresis. Cell DNA fragments assume a "comet with tail" formation on electrophoresis and are detected with an image analysis system. Alkaline assay conditions facilitate sensitive detection of double-strand and single-strand damage, as well as alkali-labile sites. Modifications to standard methodology enable detection of types of DNA damage, e.g., DNA-DNA or DNA-protein cross-links and base-oxidation.

Complementary DNA (cDNA): cDNA is DNA that is synthesised in the laboratory from mRNA by reverse transcription. A cDNA is so-called because its sequence is the complement of the original mRNA sequence.

Confounding variable: (synonym - confounder) A confounding variable is a factor that is independently associated with both an intervention or exposure and the outcome of interest. Failure to account for this will distort the observed measure of association in the statistical analysis. For example, in observational studies, cigarette smoking is a confounding variable with respect to an association between alcohol consumption and heart disease because it is a risk factor for heart disease and is associated with alcohol consumption but is not a consequence of alcohol consumption. Similarly, if people in the experimental group of a controlled trial are younger than those in the control group, age could act as a potential confounder and make it difficult to ascertain whether a lower risk of death in one group is due to the intervention or the difference in ages.

Confounding may also occur in experimental studies, where in a feed trial, unpalatability might result in reduced food consumption and weight loss, rather than weight loss occurring through toxicity.

Congeners: Related compounds varying in chemical structure that often, but not always, share biological properties.

Continuous Data: Quantitative data that can be measured and has an infinite number of possible values within a selected range.

Copy number variants (CNVs): Alterations in the DNA of a genome that results in the cell having an abnormal number of copies of one or more sections of the DNA. CNVs correspond to relatively large regions of the genome that have been deleted

(fewer than the normal number) or duplicated (more than the normal number) on certain chromosomes.

Covalent binding: Chemical bonding formed by the sharing of an electron pair between two atoms. Molecules are combinations of atoms bound together by covalent bonds (see adduct).

Critical effect size (CES): The magnitude of the adverse effect selected at which to determine the dose to serve as a point of departure in assessing the risk from exposure to a chemical. This term is often used synonymously with Benchmark Response (BMR). Choice of CES includes both statistical and toxicological considerations.

Cumulative exposure: exposure to multiple chemicals on the basis of grouping them on some common characteristic, such as mode of action, adverse effect, or inclusion in a product formulation.

P450 (CYP): An extensive family of haem-containing proteins involved in enzymic oxidation of a wide range of endogenous and xenobiotic substances and their conversion to forms that may be more easily excreted. In some cases, the metabolites produced may be chemically reactive and have increased toxicity. In other cases, the substances may be natural precursors of hormones (e.g., steroids).

Cytogenetic: Concerning chromosomes, their origin, structure and function.

(DNA) Deletion: A type of mutation where there is a loss of DNA (nucleotide base pairs) from the genome. Deletions may range in size from a single nucleotide to an entire chromosome. Such deletions may be harmless, may result in disease, or may in rare cases be beneficial.

Deoxyribonucleic acid (DNA): The carrier of genetic information for all living organisms except the group of RNA viruses. Each of the 46 chromosomes in normal human somatic cells consists of 2 strands of DNA containing an estimated 50 - 250 million nucleotides, specific sequences of which make up genes. DNA itself is composed of two interwound chains of linked nucleotides.

DNA damage: Injuries to DNA that introduce deviations from its normal, chemical structure and which may, if left unrepaired, result in a mutation or a block of DNA replication. These deviations can occur naturally or may be caused by environmental physical or chemical agents.

DNA methylation: A reversible biochemical modification of DNA more or less universally present in organisms from bacteria to humans. Methyl groups can be enzymatically added to or removed from cytosine (C). It is associated with silencing of DNA sequences.

DNA probe: A piece of single-stranded DNA, typically labelled so that it can be detected (for example, a radioactive or fluorescent label can be used), which can single out and bind with another specific piece of DNA. DNA probes can be used to

determine which sequences are present in a given length of DNA or which genes are present in a sample of DNA.

DNA repair: Processes that repair potentially damaging changes in DNA, including those induced by chemical mutagens (see mutagen.) Through the action of enzymes, individual DNA bases may be replaced, or part of a strand of DNA may be replaced, using its opposite, paired strand as a template. These processes may themselves be prone to error and result in potentially deleterious changes.

DNA repair genes: Genes which code for proteins that repair damage in DNA sequences.

DNA damage response (DDR): Cells respond to the perception of DNA damage by arresting cell-cycle progression and attempting repair: collectively these actions are known as the DNA-damage response (DDR).

DNA sequencing: process by which the sequence of nucleotides along a strand of DNA is determined. Where either the whole genome or the exome (the region which encodes proteins) is sequenced this is referred to as whole genome/exome sequencing (WGS/WES).

Dominant lethal mutation: A dominant mutation (i.e., where mutation of a single allele is sufficient to cause a change in phenotype) that causes death of an early embryo.

Dopaminergic: Releasing or involving dopamine as a neurotransmitter.

Dose: Total amount of a substance administered to, taken or absorbed by an organism. May be qualified such as external dose, absorbed dose.

Dose-response relationship: how an effect caused by a chemical changes as the dose of the [chemical](#) changes, after a certain exposure time.

Endocrine active substance (EAS): A substance that can interact or interfere with the endocrine system.

Endocrine disrupter (ED): An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny or (sub)populations.

Endonuclease: An enzyme that cleaves its nucleic acid substrate at internal sites in the nucleotide sequence.

Enterohepatic circulation: Cyclical process involving intestinal re-absorption of a substance that has been excreted through bile followed by transfer back to the liver, making it available for biliary excretion again.

Epidemiology: Study of factors determining the causes, frequency, distribution, and control of diseases in a human population.

Epigenetics: The study of heritable changes in gene function that occur without a change in the sequence of nuclear DNA and the processes involved in the unfolding development of an organism.

Epigenetic age: An estimate of biological age based on changes in epigenetic marks at particular locations along the genome.

Epigenetic drift: Divergence of the epigenome as a function of age due to stochastic changes in epigenetic marks.

Epigenetic marks: Features not directly governed by the genetic code, which include methylation of DNA and covalent modification of histone proteins. The latter may be tagged with methyl, acetyl, ubiquitin, phosphate, poly(ADP)ribose and other biochemical groups. These groups and their particular pattern of protein modification (e.g., mono-, bi-, tri-methylated at different amino acids and combinations of amino acids) modify the function of the tagged proteins and influence the way genes are expressed.

Epigenome: The comprehensive collection of genome-wide epigenetic phenomena, including DNA-methylation patterns, chromatin modifications, and non-coding RNA.

Epigenomic reprogramming: Resetting epigenetic marks so they resemble those of other cells from earlier developmental stages. This is of particular relevance for germline cells after the fusion of gametes when the genome is brought back into a "zero-state" of gene expression.

Epithelium: The tissue covering the outer surface of the body, the mucous membranes and cavities of the body.

Erythema: Reddening of the skin due to congestion of blood or increased blood flow in the skin.

Estrogen: Sex hormone or other substance capable of developing and maintaining female characteristics of the body (note UK spelling is oestrogen).

Exogenous: Arising outside the body.

Exposure Assessment: Process of measuring or estimating concentration or intensity, duration and frequency of exposure to an agent. The exposure could be via the environment, consumer products or the diet, or due to occupation.

Fetotoxic: Causing toxic, potentially lethal effects to the developing fetus.

Fibrosarcoma: A malignant tumour arising from connective tissue (see 'tumour').

First Pass Metabolism: rapid uptake and metabolism of an agent by the intestine or the liver, immediately after enteric absorption and before it reaches the systemic circulation.

Fluorescence In-Situ Hybridisation (FISH): A technique that allows individual chromosomes and their centromeres to be visualised in cells.

Forestomach: (See glandular stomach).

Free Radicals: any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital. Many radicals are unstable and highly reactive.

Full gene sequence: the complete order of bases in a gene. This order determines which protein a gene will produce.

Gavage: Administration of a liquid via a stomach tube, commonly used as a dosing method in toxicity studies.

Gene: The functional unit of inheritance: a specific sequence of nucleotides along the DNA molecule, forming part of a chromosome.

Gene expression: The process by which the information in a gene is used to create proteins or polypeptides.

Gene families: Groups of closely related genes that make similar products.

Gene mutation: A permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

Gene product: The protein or polypeptide coded for by a gene.

Genetic engineering: Altering the genetic material of cells or organisms in order to make them capable of making new substances or performing new functions.

Genetic polymorphism: a variation in germ-line DNA sequence among individuals, groups, or populations (e.g., a genetic polymorphism might give rise to blue eyes versus brown eyes, or population level differences in metabolic capacity). Genetic polymorphisms may be the result of chance processes or may have been induced by external agents (such as viruses or radiation). Generally, changes in DNA sequence which have been confirmed to be caused by external agents are called “mutations” rather than “polymorphisms”.

Genetic predisposition: susceptibility to a disease which is related to a polymorphism, which may or may not result in actual development of the disease.

Genetically modified organism (GMO): An organism which has had genetic material inserted into or removed from its cells.

Genome: All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.

Genomic DNA: The basic chromosome set consisting of a species-specific number of linkage groups and the genes contained therein.

Genomic imprinting: The phenomenon whereby a small subset of all the genes in our genome are expressed according to their parent of origin.

Genomics: The study of genes and their function.

Genotoxic: A chemical or physical agent which has the ability to induce mutations or so-called indicator effects which are mechanistically associated with the formation of mutations (e.g., induction of DNA modifications, DNA repair, or recombination). All mutagenic substances are genotoxic but not vice versa.

Genotype: The particular genetic pattern seen in the DNA of an individual. "Genotype" is generally used to refer to the particular pair of alleles that an individual possesses at a certain location in the genome. Compare this with phenotype.

Germ cells: Cells that give rise to the gametes of an organism that reproduces sexually. The cells undergo mitotic and meiotic cell division in the gonads followed by cellular differentiation into mature gametes, either oocytes or sperm.

Glandular stomach: The stomach in rodents consists of two separate regions – the forestomach and the glandular stomach. Only the glandular stomach is directly comparable to the human stomach.

Half-life: In the context of toxicokinetics, this is the time in which the concentration of a substance in vivo will be reduced by 50%, assuming a first order elimination process.

Hazard: Set of inherent properties of a substance, mixture of substances or a process involving substances that make it capable of causing adverse effects to organisms or the environment.

Health based guidance value (HBGV): A value indicating the amount of chemical in food that a person can consume on a regular basis usually over a lifetime without any significant risk to health.

Hepatic: Pertaining to the liver.

Hepatocyte: The principal cell type in the liver, possessing many metabolising enzymes (see 'metabolic activation').

Heterozygous: having two different forms (alleles) of a gene that controls a particular characteristic, one inherited from each parent, and therefore able to pass on either form.

Histone methylation: The modification of certain amino acids in a histone protein by the addition of methyl groups.

Histone modification: Covalent post-translational modifications to histone proteins including methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation, which regulate gene expression. The modifications made to histones can impact gene expression by altering chromatin structure.

Histone tails: A structural aspect of histones that are major targets for post-translational modifications of histones (see Histone modifications).

Hodgkin's lymphoma: Cancer of the lymphatic system.

Homeostatic: Any self-regulation process by which biological systems tend to maintain stability while adjusting to conditions that are optimal for survival.

Horizon scanning: The systematic examination of potential threats, opportunities and likely future developments, which are at the margins of current thinking and planning. Horizon scanning may explore novel and unexpected issues, as well as persistent problems and trends. Overall, horizon scanning is intended to improve the robustness of policies and the evidence base.

Hypoxanthine-guanine Phosphoribosyltransferase (HPRT) assay:

This assay uses cultured mammalian somatic cells to detect mutagenic agents. The principle of the method relies on the fact that mutations (caused by mutagens) destroy the functionality of the HPRT gene or protein, which is detected by using a toxic analogue. The HPRT-mutants are viable colonies that can be scored.

Hypoxanthine-guanine Phosphoribosyltransferase (HPRT) gene:

A protein coding gene. This transferase allows cells to recycle purines, a building block of DNA and RNA.

Hypermethylation: Increase in the methylation of cytosine-guanosine base pairs in regulatory regions of DNA.

Hyperplasia: An increase in the size of an organ or tissue due to an increase in the number of cells through cell division.

Hypertrophy: An increase in the size of an organ or tissue due to an increase in the volume of individual cells within it.

Hypomethylation: The loss of the methyl group in 5-methylcytosine nucleotides in DNA. Hypomethylation can be used to describe the unmethylated state of specific nucleotides or as a general phenomenon affecting large parts of the genome.

Idiosyncrasy: Specific (and usually unexplained) reaction of an individual to e.g., a chemical exposure to which most other individuals do not react at all. General allergic reactions do not fall into this category.

In silico: a term used to describe a computerised analysis of the structure of a chemical to assess its potential hazard.

In situ hybridisation (ISH): Use of a DNA or RNA probe to detect the presence of the complementary DNA sequence in cloned bacterial or cultured eukaryotic cells.

In vitro: A Latin term used to describe studies of biological material outside the living animal or plant (literally “in glass”).

In vivo: A Latin term used to describe studies in living animals or plants (literally “in life”).

Incidence: Number of discrete events, for example new cases of illness occurring during a given period in a specific population.

(Enzyme) Inducing agent: A chemical which, when administered to an animal, causes an increase in the expression of a particular enzyme. For example, chlorinated dibenzodioxins are inducing agents which act via the Ah-receptor (qv) to induce P450 (qv) CYP1A1.

Intraperitoneal: Within the abdominal cavity.

Isomer: Isomers are two or more chemical compounds with the same molecular formula but having different properties owing to a different arrangement of atoms within the molecule.

Key event: An empirically observable precursor step that is itself a necessary element of an AOP or MOA. A key event is a necessary, though usually not a sufficient, step in a process that results in an adverse outcome.

kilobase (kb): A length of DNA equal to 1000 nucleotides.

Knockout animals: Genetically engineered animals in which one or more genes, usually present and active in the normal animal, have been eliminated or inactivated.

LC50/LD50: The concentration or dose that causes death in 50% of a group of experimental animals to which it is administered. It can be used to assess the acute toxicity of a compound but is being superseded by more refined methods.

Less than lifetime (LTL) exposure: any exposure that is not continuous daily exposure, for example, short-term, intermediate or intermittent, or a combination of these.

Leukaemia: A group of neoplastic disorders (see tumour) affecting blood-forming elements in the bone marrow, characterised by uncontrolled proliferation and disordered differentiation or maturation. Examples include the lymphocytic leukaemia's which develop from lymphoid cells and the myeloid leukaemia's which are derived from myeloid cells (producing red blood cells, mainly in bone marrow).

Ligand: A molecule which binds to an allosteric binding site in a protein, such as a receptor.

Lipids: Fats, substances containing a fatty acid and soluble in alcohols or ether, but insoluble in water.

Lipophilic: 'Lipid liking' - a substance which has a tendency to partition into fatty materials.

Lowest observed adverse effect level (LOAEL): The lowest administered dose at which a statistically significant adverse effect, relative to that of the control, has been observed. Also given as LOEL when no 'adverse' effects are seen.

Lymphocyte: A type of white blood cell that plays central roles in adaptive immune responses.

Lymphoma: Malignant tumours arising from lymphoid tissues. They are usually multifocal, involving lymph nodes, spleen, thymus and sometimes bone marrow, and other sites outside the anatomically defined lymphoid system. (See also 'tumour').

Malformations: The inheritance of an abnormal or anomalous formation of tissues and organs often referred to as a deformity.

Malignant tumour (synonym: cancer): A tumour (qv) composed of increasingly abnormal cells in term of their form and function. Some well differentiated examples still retain characteristics of their tissues of origin but these are progressively lost in moderately and poorly differentiated malignancies. Most malignant tumours grow rapidly, spread progressively through adjacent tissues and metastasise to distant sites.

Margin of exposure (MOE) approach: A methodology that allows the comparison of the risks posed by substances when it is not possible or not appropriate to establish a HBGV. This would include substances that are genotoxic and carcinogenic, and contaminants for which there is insufficient information to establish a Tolerable Daily Intake The MOE approach uses a reference point (or POD), often taken from an animal study, corresponding to a dose that causes no or a low response (for example the NAOEL, LOAEL, BMDL10). This reference point is then compared with various exposure estimates in humans. The lower the MOE, the greater the concern. The MOE considered to be of low or negligible concern is context specific. In general, for substances that are genotoxic and carcinogenic, and MOE of >10,000, when based on a reference point from an animal study, would be considered of low concern. For a non-genotoxic, non-carcinogenic contaminant, an MOE of > 100 would be considered of negligible concern.

Margin of safety (MOS) approach: A methodology used to assess relative risk when there is exceedance of a HBGV. The MOS is expressed as the ratio of the HBGV to measured or estimated exposure. The lower the MOS is below 1, the greater the concern.

Maximum tolerated dose: The MTD for a long-term study of carcinogenicity is a dose that produces minimal signs of toxicity on repeated administration, meaning no more than a 10% weight decrement, as compared to the appropriate control groups; and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other

than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span.

Mechanism of action: an understanding of the molecular basis for an effect and its detailed description, so causation can be established in molecular terms.

Meiosis: The process of cell division in sexually reproducing organisms that reduces the number of chromosomes in reproductive cells from diploid to haploid leading to the production of gametes in animals and spores in plants. During the first meiotic division there is homologue pairing, efficient intergenic recombination between homologues during pairing, and the suppression of sister chromatid separation. S phase is absent at the start of the second meiotic division. Thus, the outcome of meiosis should be four genetically unique haploid cells.

Messenger RNA (mRNA): The DNA of a gene is transcribed (see transcription) into mRNA molecules, which then serve as a template for the synthesis of proteins.

Meta-analysis: In the context of epidemiology, a statistical analysis of the results from independent studies, which aims to produce a single estimate of an effect.

Metabolic activation: Metabolism of a compound leading to an increase in its activity, whether beneficial (e.g., activation of a pro-drug) or deleterious (e.g., activation to a toxic metabolite).

Metabolic activation system: A cell-free preparation (e.g., from the livers of rats pre-treated with an inducing agent (qv)) added to in vitro tests to mimic the metabolic activation typical of mammals.

Metabolism: Chemical modification of a compound by enzymes within the body, for example by reactions such as hydroxylation (see P450), epoxidation or conjugation. Metabolism may result in activation, inactivation, change in activity, accumulation or excretion of the compound.

Metabolite: Product formed by metabolism of a compound.

Metabolomics: The measurement of the amounts (concentrations) and locations of all metabolites in a cell.

Metabonomics: Metabonomics is a subset of metabolomics and is defined as the quantitative measurement of the multiparametric metabolic responses of living systems to pathophysiological stimuli or genetic modification.

Metaphase: Stage of cell division (mitosis and meiosis) during which the chromosomes are arranged on the equator of the nuclear spindle (the collection of microtubule filaments which are responsible for the movement of chromosomes during cell division). As the chromosomes are most easily examined in metaphase, cells are arrested at this stage for microscopical examination for chromosomal aberrations (qv) - known as metaphase analysis.

Metastasis: The process whereby malignant cells become detached from the primary tumour mass, disseminate (mainly in the blood stream or in lymph vessels) and seed out in distant sites where they form secondary or metastatic tumours. Such tumours tend to develop at specific sites and their anatomical distribution is often characteristic, i.e., it is non-random.

Microbiome (Human): Human microbiome is the full array of microorganisms (the microbiota) that live on and in humans and, more specifically, the collection of microbial genomes that contribute to the broader genetic portrait, or metagenome, of a human. Often a subset of the microbiome is the subject of interest, for example the intestinal or dermal microbiome.

Micronuclei: Whole or fragmented chromosomes that fail to segregate normally during cell division and may be lost from the main nuclei but remain in the body of the cell forming micronuclei. Centromere positive micronuclei contain DNA and/or protein material derived from the centromere. The presence of centromere positive micronuclei following exposure to chemicals in vitro or in vivo can be used to evaluate the aneugenic potential of chemicals.

Minimal risk level: defined in this document as an estimate of daily human exposure to a chemical, identified by expert judgement, that is likely to be associated with a negligible risk of carcinogenic effect over a specified duration of exposure (usually a lifetime).

Mitogen: A stimulus which provokes cell division in somatic cells.

Mitosis: The process in cell division in somatic cells by which the nucleus divides, typically consisting of four stages, prophase, metaphase, anaphase, and telophase, and normally resulting in two new nuclei, each of which contains a complete copy of the parental chromosomes. The outcome of mitosis should be two genetically identical diploid cells.

Mode of Action: a biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data. It describes key cytological and biochemical events, i.e., those that are both measurable and necessary to the observed outcome, in a logical framework. It contrasts with mechanism of action.

Mode of genotoxic action (MoGA): The mode of action of a genotoxicant refers to the underlying events involved in the process whereby the chemical induces genotoxic effects. In order for a specific mode of action to be supported there needs to be evidence from robust mechanistic data to establish a biologically plausible explanation. Mode of genotoxic action should be distinguished from the term mechanism of action. The latter relates to having sufficient understanding of the molecular basis of the chemical genotoxicity to establish causality. Thus, mechanism of action is at the other end of a continuum from little or no evidence of mode of genotoxic action to scientific proof of mechanism of action.

Molecular initiating event (MIE): the initial point of chemical/stressor interaction at the molecular level within the organism that results in a perturbation that starts the AOP.

Mouse lymphoma assay: An in vitro assay for gene mutation in mammalian cells using a mouse lymphoma cell line L5178Y, which is heterozygous for the gene (carries only one functional allele rather than a pair) for the enzyme thymidine kinase (TK+/-). Mutation of that single gene is measured by resistance to toxic trifluorothymidine. Mutant cells produce two forms of colony - large, which represent mutations within the gene and small, which represent large genetic changes in the chromosome such as chromosome aberrations. Thus, this assay can provide additional information about the type of mutation which has occurred if colony size is scored.

Mucosal: Regarding the mucosa or mucous membranes, consisting of epithelium containing glands secreting mucus, with underlying layers of connective tissue and muscle.

Multigenerational effects: Effect seen in exposed generations, including those that may have been exposed in utero, as offspring or gametes. For effects in unexposed generations see 'Transgenerational effects'.

Murine: Often taken to mean "of the mouse", but strictly speaking means of the Family Muridae which includes rats and squirrels.

Mutagen: is a physical or chemical agent that changes the genetic information (usually DNA) of an organism that can be inherited by daughter cells.

Mutation: A permanent change in the amount or structure of the genetic material in an organism or cell, which can result in a change in phenotypic characteristics. The alteration may involve a single gene, a block of genes, or a whole chromosome. Mutations involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Changes involving whole chromosomes may be numerical or structural. A mutation in the germ cells of sexually reproducing organisms may be transmitted to the offspring, whereas a mutation that occurs in somatic cells may be transferred only to descendent daughter cells.

Mutational signatures: Mutational signatures are characteristic profiles of mutation types arising from specific mutagenesis processes such as DNA replication infidelity, exogenous and endogenous genotoxins exposures, defective DNA repair pathways and DNA enzymatic editing.

Mycotoxin: Toxic compound produced by a fungus.

Nanomaterial: A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.

Neoplasia: the abnormal proliferation of benign or malignant cells.

Neoplasm: See 'tumour'.

Neoplastic: Abnormal cells, the growth of which is more rapid than that of other cells of the same tissue type.

Neural tube defect (NTD): Is a birth defect in which an opening in the spine or cranium remains from early in human development.

Neurobehavioural: Of behaviour determined by the nervous system.

Neurotransmitter: A chemical that is released from a nerve cell which thereby transmits an impulse from a nerve cell to another nerve, muscle, organ, or other tissue. A neurotransmitter is a messenger of neurologic information from one cell to another.

No observed adverse effect level (NOAEL): The highest administered dose at which no statistically significant adverse effect has been observed in comparison to the control. Also given as NOEL when no 'adverse' effects are seen.

Non-Hodgkin lymphomas: (NHLs) are a diverse group of hematologic cancers which encompass any lymphoma other than Hodgkin's Lymphoma.

No observed genotoxic effect level (NOGEL): This is the highest experimental dose level where no statistically significant increase in the genotoxic effect measured in the study is identified.

Nucleic acid: One of the family of molecules which includes the DNA and RNA molecules. Nucleic acids were so named because they were originally discovered within the nucleus of cells, but they have since been found to exist outside the nucleus as well.

Nucleosome: A repeating subunit of DNA packaging consisting of DNA wound in sequence around histone proteins.

Nucleotide: the "building block" of nucleic acids, such as the DNA molecule. A nucleotide consists of a nucleoside attached a phosphate group. A nucleoside comprises one of four bases - adenine, guanine, cytosine, or thymine - attached to a sugar group. In DNA the sugar group is deoxyribose, while in RNA (a DNA-related molecule which helps to translate genetic information into proteins), the sugar group is ribose, and the base uracil substitutes for thymine. Each group of three nucleotides in a gene is known as a codon. A nucleic acid is a long chain of nucleotides joined together, and therefore is sometimes referred to as a "polynucleotide."

Null allele: Mutations that result in absence of gene product or a non-functional product.

Null hypothesis: type of conjecture used in statistical tests, which are formal methods of reaching conclusions or making decisions on the basis of data. In toxicology, a common null hypothesis is that there is no effect of treatment with a substance. Statistical testing may enable a conclusion that this is most likely incorrect, i.e., the null hypothesis is rejected with a stated probability of error, or it is not possible to reach a conclusion. It is not possible by conventional statistical testing to prove the null hypothesis is most likely correct, i.e., that there is no effect. This is the axiomatic difficulty of “proving a negative”.

Odds ratio (OR): The odds of disease in an exposed group divided by the odds of disease in an unexposed group.

Oedema: Excessive accumulation of fluid in body tissues.

Oligonucleotide: A molecule made up of a small number of nucleotides, typically fewer than 25.

‘Omics’ technologies: A scientific subdiscipline that combines the technologies of genomics and bioinformatics to identify and characterise mechanisms of action of known and suspected toxicants. The collective term ‘omics’ refers to the genomic (DNA sequence analysis) and post-genomic (e.g., transcriptomics, proteomics, metabolomics, epigenomics) technologies that are used for the characterisation and quantitation of pools of biological molecules (e.g. DNA, mRNAs, proteins, metabolites), and the exploration of their roles, relationships and actions within an organism.

Oncogene: A gene which is associated with the development of cancer (see proto-oncogene).

Pharmacodynamics: The process of interaction of drugs with target sites and the subsequent reactions leading to the desired biological effects (see toxicodynamics).

Pharmacokinetics: Description of the fate of drugs in the body, including a mathematical account of their absorption, distribution, metabolism and excretion (see toxicokinetics).

Pharmacogenomics: The science of understanding the correlation between an individual patient's genetic make-up (genotype) and their response to drug treatment. Some drugs work well in some patient populations and not as well in others. Studying the genetic basis of patient response to therapeutics allows drug developers and medical practitioners to design and use therapeutic treatments more effectively.

Phenotype: The observable physical, biochemical and physiological characteristics of a cell, tissue, organ or individual, as determined by its genotype and the environment in which it develops.

Phenotypic change: A change in the observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.

Physiologically based pharmacokinetic (PBPK) model: A mathematical model which is used to predict the absorption, distribution, metabolism and excretion of a chemical substance in humans.

Phytoestrogen: Any plant substance or metabolite that can mimic or modulate the actions of endogenous oestrogens, usually by binding to oestrogen receptors, and which can therefore induce biological responses.

Pig-A gene mutation assay: An assay which utilises the Pig-A gene which codes for one subunit of a glycosylphosphatidyl inositol anchor protein. Loss of function arising from Pig-A mutations can readily be assessed using straightforward immunochemistry and flow cytometric methods, thus making it useful to measure gene mutations induced by chemicals or radiation.

Plasmid: A structure composed of DNA that is separate from the cell's genome (qv). In bacteria, plasmids confer a variety of traits and can be exchanged between individuals, even those of different species. Plasmids can be constructed and manipulated in the laboratory to deliver specific genetic sequences into a cell.

Point of departure: a dose associated with a defined level of effect, which can be determined empirically or by modelling dose-response data from experimental studies, from which a health-based guidance value can be established, or which can be used for a margin of exposure assessment. Examples include a BMDL, NOAEL or LOAEL.

Polymer: A very large molecule comprising a chain of many similar or identical molecular sub units (monomers) joined together (polymerised). An example is the polymer glycogen, formed from linked molecules of the monomer glucose.

Polymerase chain reaction (PCR): A method for creating millions of copies of a particular segment of DNA. PCR can be used to amplify the amount of a particular DNA sequence until there are enough copies available to be detected.

Polymorphism: (see genetic polymorphism)

³²P postlabelling assay: An experimental method designed to measure low levels of DNA adducts induced by chemical treatment. It involves labelling of adducted nucleosides from digested DNA with ³²P and their quantification following chromatographic separation.

Prevalence: The number of discrete cases, for example of a disease, that are present in a population at a given time.

Primer: Short pre-existing polynucleotide chain to which new deoxyribonucleotides can be added by DNA polymerase.

Primordial germ cells: Highly specialised cells that are precursors of gametes, which, following meiosis, develop as haploid sperm and eggs that generate a new organism upon fertilisation.

Proteomics: The analysis of the entire protein complement of a cell, tissue, or organism under a specific, defined set of conditions.

Proto-oncogene: One of a group of normal genes that are concerned with the control of cellular proliferation and differentiation. They can be activated in various ways to forms (oncogenes) which are closely associated with one or more steps in carcinogenesis. Activating agents include chemicals and viruses. The process of proto-oncogene activation is thought to play an important part at several stages in the development of tumours.

Quantal Data: When the response for an individual unit (well, animal etc) is a binary value, such as alive / dead, or response / no response, the data are treated as quantal. The responses are assumed to follow a binomial distribution within each dose group. This assumption is required for the calculations of confidence intervals and the p values resulting from statistical tests.

ras oncogene: The Ras protein family are a class of protein called small GTPase and have important roles in cell signalling. The ras gene is the most common oncogene involved in human cancer - mutations that permanently activate ras are found in 20-25% of all human tumours and up to 90% in certain types of cancer (e.g., pancreatic cancer).

Receptor: A small, discrete protein in the cell membrane or within the cell with which specific molecules interact to initiate a change in the working of a cell.

Recombinant DNA: DNA molecules that have been created by combining DNA from more than one source.

Reference nutrient intake (RNI): An amount of the nutrient that is sufficient, or more than sufficient, to ensure adequate nutrient function for most (usually at least 97%) people in a group. If the average intake of a group is at the RNI, then the risk of deficiency in the group is very small.

Regulatory gene: A gene which controls the protein-synthesising activity of other genes.

Relative potency factor (RPF): The toxic potency of a substance expressed relative to that of an index chemical to enable cumulative risk assessment (qv). The RPF is similar to the TEF (qv) but is used when the information on common MIEs, toxicokinetics and outcomes of the members of an assessment group is less reliable than that required for application of the TEF approach.

Relative risk: A measure of the association between exposure and outcome. The rate of disease in the exposed population divided by the rate of disease among the unexposed population in a cohort study or a population-based case control study. A

relative risk of 2 means that the exposed group has twice the disease risk compared to the unexposed group.

Reporter gene: A gene that encodes an easily assayed product that is coupled to the upstream sequence of another gene and transfected (qv) into cells. The reporter gene can then be used to see which factors activate response elements in the upstream region of the gene of interest.

Risk: Probability that a harmful event (death, injury or loss) arising from exposure to a chemical or physical agent may occur under specific conditions.

Risk assessment: process of evaluating a potential hazard, likelihood of suffering, or any adverse effects from certain human activities. Comprised of the four aspects, hazard identification, hazard characterisation, exposure assessment and risk characterisation. Can be carried out retrospectively or prospectively.

Risk management: process designed to identify, contain, reduce, or eliminate the potential for harm to the human population; usually concerned with the delivery system and site rather than performance.

Ribonucleic acid (RNA): a molecule similar to DNA, in that it is a nucleic acid comprised of a chain of nucleotides. However, unlike DNA, RNA exists as a single-stranded chain. RNA has various biological roles in coding, decoding, regulation and expression of genes.

Sarcoma: cancer that arises from transformed cells of mesenchymal (connective tissue) origin.

Serotonergic: Denoting a nerve ending that releases and or stimulated by serotonin.

Signal induction pathway: The molecular pathways that signal (i.e., turn on or off) biochemical pathways or biological functions (e.g., biochemical pathways leading to nerve conduction).

Single nucleotide polymorphism (SNP): DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. For example, a SNP might change the DNA sequence AAGGCTAA to ATGGCTAA.

Strand breaks: Relating to DNA, a single strand break occurs when there is a break in double-stranded DNA in which only one of the two strands has been cleaved; the two strands have not separated from each other. Double strand breaks occur when both strands in the double helix are severed and are particularly hazardous to the cell because they can lead to genome rearrangements.

Sister chromatid exchange (SCE): Exchange of genetic material between two subunits of a replicated chromosome.

Somatic cells: Any biological cell that forms part of the body of an organism, excluding reproductive cells and undifferentiated stem cells.

Stakeholder: A person or organisation representing the interests and opinions of a group with an interest in the outcome of (for example) a review or policy decision.

Statistical significance: a conclusion drawn when, after carrying out a statistical test of the null hypothesis of no effect, the hypothesis is considered unlikely to be true. The criterion for the decision is often a probability (p) value, chosen to be, but not necessarily, $p < 0.05$.

Stem cell: an unspecialized cell capable of perpetuating itself through cell division and having the potential to give rise to differentiated cells with specialized functions.

Suppressor gene: A gene which helps to reverse the effects of damage to an individual's genetic material, typically these are effects which might lead to uncontrolled cell growth (as would occur in cancer). A suppressor gene may, for example, code for a protein which checks genes for misspellings, and/or which triggers a cell's self-destruction if too much DNA damage has occurred.

Systematic review: A formalised review that has been prepared using a documented systematic approach to minimising biases and random errors.

Systems biology: The computational and mathematical analysis and modelling of complex biological systems.

Systems toxicology: The integration of classical toxicology with quantitative analysis of large networks of molecular and functional changes occurring across multiple levels of biological organisation.

T25: the dose eliciting a 25% increase in the incidence of a specific tumour above the background level.

TD₅₀: For any particular sex, strain, species and set of experimental conditions, the TD₅₀ is the dose rate (in mg/kg body weight/day) that, if administered chronically for a standard period - the "standard lifespan" of the species-will halve the mortality-corrected estimate of the probability of remaining tumourless throughout that period.

Teratogen: A substance that can cause congenital malformations (structural defects) in a developing fetus following maternal exposure.

Testicular dysgenesis syndrome (TDS): The hypothesis that maldevelopment (dysgenesis) of the fetal testis results from hormonal or other malfunctions of the testicular somatic cells which in turn predispose a male to the disorders that comprise the TDS, i.e., congenital malformations (cryptorchidism and hypospadias) in babies and testis cancer and low sperm counts in young men.

Threshold: the level of dose or exposure below which there is no effect above that in the control group or population. There are several different uses of the term threshold, for example observable threshold, biological threshold, population threshold.

Threshold of toxicological concern (TTC): a pragmatic, scientifically valid methodology to prioritise substances of unknown toxicity found in food for further evaluation. It is used when there are limited chemical-specific toxicity data and can be used for substances with or without structural alerts for genotoxicity and for cancer and non-cancer endpoints.

Tolerable daily intake (TDI): An estimate of the amount of contaminant, expressed on a body weight basis (e.g., mg/kg bodyweight), that can be ingested daily over a lifetime without appreciable health risk. The term is preferred for substances that are unintentionally present.

Tolerable upper level (TUL): The highest level of nutrient that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the TUL, the risk of adverse effects increases.

Toxic equivalency factor (TEF): A measure of relative toxicological potency of a chemical compared to a well characterised reference compound. TEFs can be used to sum the toxicological potency of a mixture of chemicals which are all members of the same chemical class, having common structural, toxicological and biochemical properties. TEF systems have been published for the chlorinated dibenzodioxins, dibenzofurans and dioxin-like polychlorinated biphenyls, and for polycyclic aromatic hydrocarbons.

Total toxic equivalent (TEQ): Is a method of comparing the total relative toxicological potency within a sample. It is calculated as the sum of the products of the concentration of each congener multiplied by the toxic equivalency factor (TEF).

Toxicodynamics: The process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

Toxicogenic: producing or capable of producing toxins, e.g., a fungal strain.

Toxicokinetics: The description of the fate of potentially toxic chemicals in the body, including a mathematical account of their absorption, distribution, metabolism and excretion, particularly at doses that are toxic. (see pharmacokinetics)

Transcription: the process during which the information in a piece of DNA (qv) is used to construct an mRNA (qv) molecule.

Transcriptomics: Techniques used to identify mRNA from actively transcribed genes.

Transgenerational effects: Effects seen in generations that have not been exposed, either directly to the substance under consideration or indirectly as offspring or gametes via parental exposure. For effects in exposed populations, see 'multigenerational effects'.

Transfer RNA (tRNA): RNA molecules which bond with amino acids and transfer them to ribosomes, where protein synthesis is completed.

Transfection: A process by which exogenous genetic material (DNA or RNA) is introduced into a cell with the object of altering the phenotype or genotype of the cell.

Transgenic: Genetically modified to contain genetic material from another species (see also genetically modified organism).

Transgenic animal models: Animals which have extra (exogenous) fragments of DNA incorporated into their genomes. This may include reporter genes to assess in-vivo effects such as mutagenicity in transgenic mice containing a recoverable bacterial gene (lacZ or lac I). Other transgenic animals may have alterations of specific genes believed to be involved in disease processes (e.g., cancer). For example, strains of mice have been bred which carry an inactivated copy of the p53 tumour suppressor gene, or an activated form of the ras oncogene which may enhance their susceptibility of the mice to certain types of carcinogenic chemicals.

Translation: In molecular biology, the process during which the information in mRNA molecules is used to construct proteins.

Tumour (Synonym - neoplasm): A mass of abnormal, disorganised cells, arising from pre-existing tissue, which are characterised by excessive and uncoordinated proliferation and by abnormal differentiation. Benign tumours show a close morphological resemblance to their tissue of origin; grow in a slow expansile fashion; and form circumscribed and (usually) encapsulated masses. They may stop growing and they may regress. Benign tumours do not infiltrate through local tissues, and they do not metastasise (qv). They are rarely fatal. Malignant tumours (synonym - cancer) resemble their parent tissues less closely and are composed of increasingly abnormal cells in terms of their form and function. Well differentiated examples still retain recognisable features of their tissue of origin, but these characteristics are progressively lost in moderately and poorly differentiated malignancies: undifferentiated or anaplastic tumours are composed of cells which resemble no known normal tissue. Most malignant tumours grow rapidly, spread progressively through adjacent tissues and metastasise to distant sites. Tumours are conventionally classified according to the anatomical site of the primary tumour and its microscopical appearance, rather than by cause. Benign tumours may evolve to the corresponding malignant tumours; examples involve the adenoma → carcinoma sequence in the large bowel in humans, and the papilloma → carcinoma sequence in mouse skin.

Tumour initiation: A term originally used to describe and explain observations made in laboratory models of multistage carcinogenesis, principally involving repeated applications of chemicals to the skin of mice. Initiation, in such contexts, was the first step whereby small numbers of cells were irreversibly changed or initiated. Subsequent, separate events (see tumour promotion) resulted in the development of tumours. It is now recognised that these early, irreversible heritable changes in initiated cells were due to genotoxic damage, usually in the form of somatic mutations and the initiators used in these experimental models can be regarded as genotoxic carcinogens.

Tumour microenvironment: This is a complex system of many cell types, including cancer cells, fibroblasts, endothelial cells, leukocytes and antigen-

presenting cells, together with connective tissue. The microenvironment is integral in determining the functionality, physiology and spread (metastasis) of cancer.

Tumour promotion: Originally used, like 'tumour initiation' to describe events in multistage carcinogenesis in experimental animals. In that context, promotion is regarded as the protracted process whereby initiated cells undergo clonal expansion to form overt tumours. The mechanisms of clonal expansion are diverse, but include direct stimulation of cell proliferation, repeated cycles of cell damage and cell regeneration and release of cells from normal growth-controlling mechanisms. Initiating and promoting agents were originally regarded as separate categories, but the distinction between them is becoming increasingly hard to sustain. The various modes of promotion are non-genotoxic, but it is incorrect to conclude that 'non-genotoxic carcinogen' and 'promoter' are synonymous.

Uncertainty factor: Value used in extrapolation from a reference point (or POD), determined in experimental animals, to humans (assuming that humans may be more sensitive) or from a sub-population of individuals to the general population: for example, a value applied to the NOAEL to establish an ADI or TDI. The value depends on the size and type of population to be protected and the quality of the toxicological information available.

Unscheduled DNA synthesis (UDS): DNA synthesis that occurs at some stage in the cell cycle other than the S period (the normal or 'scheduled' DNA synthesis period), in response to DNA damage. It is usually associated with DNA repair.

Volume of distribution: Apparent volume of fluid required to contain the total amount of a substance in the body at the same concentration as that present in the plasma, assuming equilibrium has been attained.

Weight of evidence: This approach uses a combination of several independent sources of evidence (e.g., toxicological or genotoxicity data) to arrive at a conclusion regarding potential hazard (such as mutagenicity).

WHO-TEQs: The system of Toxic Equivalency Factors (TEFs) used in the UK and a number of other countries to express the concentrations of the less toxic dioxin-like compounds (16 PCDDs/PCDFs and 12 PCBs) as a concentration equivalent to the most toxic dioxin 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is that set by the World Health Organisation (WHO), and the resulting overall concentrations are referred to as WHO-TEQs (Total toxic equivalents) (see also Toxic Equivalency Factor).

Xenobiotic: A chemical foreign to the biologic system.

Xenoandrogen: A 'foreign' compound with androgenic activity (see androgen).

Xenoestrogen: A 'foreign' compound with oestrogenic activity (see oestrogen).

Organisational abbreviations

COC: Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment: is an independent scientific committee that provides advice the government and government agencies on whether substances are likely to cause cancer.

COM: Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment: is an independent scientific committee that assesses and advises the government and government agencies on mutagenic risks to humans.

COT Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: is an independent scientific committee that provides advice to the government and government agencies on matters concerning the toxicity of chemicals.

EFSA European Food Safety Authority

Expert Group on Vitamins and Minerals (EVM): An independent UK expert advisory committee which was asked to advise on safe levels of intakes of vitamins and minerals in food supplements and fortified foods.