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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.

Malignancy: [See 'tumour'](#).

Margin of exposure (MOE) approach: A methodology that allows the comparison of the risks posed by different genotoxic and carcinogenic substances. The MOE approach uses a reference point, often taken from an animal study and corresponding to a dose that causes a low but measurable response in animals. This reference point is then compared with various dietary intake estimates in humans, taking into account differences in consumption patterns.

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 cytochrome P450), epoxidation or conjugation. Metabolism may result in activation, inactivation, 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: Techniques available to identify the presence and concentrations of metabolites in a biological sample.

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; 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: Isolated or broken chromosome fragments which are not expelled when the nucleus is lost during cell division, 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 can be used to evaluate the aneugenic (qv) potential of chemicals.

Micronucleus test: See Micronuclei.

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 type of cell division which occurs in somatic cells when they proliferate. Each daughter cell has the same complement of chromosomes as the parent cell.

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 gene 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.

Mouse spot test: An *in vivo* test for mutation, in which pregnant mice are dosed with the test compound and mutations are detected by changes (spots) in coat colour of the offspring. Mutations in the melanocytes (skin pigment cells) of the developing fetus are measured.

Mucosal: Regarding the mucosa or mucous membranes, consisting of epithelium (qv) 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.