Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC)

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The Use of Biomarkers in Carcinogenic Risk Assessment


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The Use of Biomarkers in Carcinogenic Risk Assessment

Introduction

1. A biomarker is any substance, structure or process that can be measured in an organism, related to a specific exposure or effect or which can influence the incidence of the effect. Biomarkers can provide valuable information to aid chemical risk assessment processes and are used as investigative tools in both animal and human studies which aim to evaluate carcinogenic hazards and risk. The overarching summary Guidance Statement (G01) provides the Committee’s views on the general principles relating to carcinogenic hazard and risk assessment and a background to the individual components of the risk assessment process and how these are integrated. This statement aims to provide detail of how biomarkers are utilised within the individual components of the risk assessment process.

2. The Committee recommends a four-stage approach to the risk assessment of chemical carcinogens which is based on the widely adopted paradigm proposed by the National Academy of Sciences (US National Academy of Sciences, 1983). This is summarised as follows:

![Figure 1: Four stage evaluation strategy for the risk assessment process of carcinogenic hazard](image-url)
3. Within exposure assessment, biomarkers can be used (usually) to establish recent exposures to, and uptake of, actual or putative carcinogens in human populations or experimental animals. Within hazard assessment, biomarkers may be used to quantitatively associate a dose or exposure with either a precursor carcinogenic effect or the probability of a disease outcome. In this context, biomarkers can provide specific evidence that a chemical has the potential to cause a carcinogenic effect and may also provide information on mode of action. Therefore, biomarkers provide a range of possible measurements from systemic exposure through to resulting causal events in the process of carcinogenesis.

4. For the purposes of this document, biomarkers will be broadly characterised as those of exposure and those of effect, although the distinction between these two is not always clear-cut. Biomarkers in the context of carcinogenicity can mean proof of exposure to a carcinogen, detection of a reaction product or an indication that a preliminary genotoxic event or actual DNA damage has occurred. Other types of biomarkers exist, for example biomarkers of susceptibility, which are increasingly being introduced as interpretative aids to epidemiological investigations of chemical-induced carcinogenesis.

5. When utilising biomarker data, it is important to consider that there is usually a long latency period between exposure to the carcinogen and the clinical onset of cancer. Currently, established biomarkers of exposure often represent recent exposure but some which show organ or tissue retention can be used to assess long-term exposure. In the future permanent changes in gene expression and epigenetic changes may provide new biomarkers of exposure and effect that will have utility in longer term epidemiological studies.

6. Biomarkers are powerful tools for investigating the mode of carcinogenic action (MOA) and can be incorporated into animal studies for this purpose. Indeed, biomarkers, where a clear rationale for the alteration of the level of biomarker with the underlying latent variable, can be useful to discern mechanisms of action. Conversely, knowledge of MOA may help in the development of better biomarkers for use in human exposure scenarios.

7. The Committee has a role in evaluating the entire spectrum of biomarkers including the development, validation and practicality of new techniques and the applicability and interpretation of well-established methods.

Biomarker characterisation and validation

8. Biomarkers must be appropriately characterised and validated before conclusions are drawn from their use. There are a number of criteria that should be considered when selecting and validating suitable biomarkers for use in human biomonitoring studies (IPCS, 2001; Albertini et al., 2000; Angerer et al., 2007). These include:
   - selection of a suitable biological matrix
ability to reflect internal exposure and/or biological/biochemical effects with a clear relationship between dose, exposure and biomarker level
suitable and reliable analytical method with adequate evaluation of the sensitivity and specificity (limit of detection, precision and accuracy)
knowledge of the half-life and kinetics of the biomarker including an understanding of biomarker stability post-collection
investigation of intra- and inter-individual variation in a non-exposed population (i.e. background), and the reference and limit values enabling interpretation of results.

9. Biomarkers used in animal studies must also be suitably characterised and validated and this should be based on the principles detailed for human biomarkers. The validation of biomarkers in epidemiological studies should also utilise ACCE criteria (analytical validity, clinical validation, clinical utility and ethical, legal and social implications) (Gallo et al., 2008). In relation to biomarkers, the STrengthening the Reporting of OBservational studies in Epidemiology – Molecular Epidemiology (STROBE-ME) initiative provides guidance on reporting of factors such as collection, handling and storage of biological samples and aspects such as method reliability, biomarker validation and study design (Gallo et al., 2011). The STROBE-ME initiative provides standardised guidelines and a ‘checklist’ for the reporting of biomarker and molecular epidemiology studies (see http://www.equator-network.org/reporting-guidelines/strobe-me/, accessed 24/04/17).

Biomarkers of exposure

10. The objective of human exposure assessment is to estimate probable exposure by determining exposure routes, source, magnitude and duration of contact with the chemical of concern (Angerer et al., 2007). However, epidemiological studies often have major limitations related to measurement of exposure to carcinogens over long periods, for example inaccuracies as a result of recall bias in certain study designs. Consequently, in these studies, exposure assessment is frequently identified as the main area of uncertainty in the overall risk assessment process. Although the alternative approach of personal monitoring (e.g. dermal patch studies) provides ways to measure exposure directly, assumptions need to be made about the relationship between results from short-term sampling and predicted long-term exposure. To help overcome these limitations, biomarkers of exposure were developed (Angerer et al., 2007). Approaches used in exposure assessment and the characterisation of uncertainties and variability in the resulting estimates have been extensively reviewed elsewhere (Angerer et al., 2007, IPCS, 1999).

11. Biomarkers of exposure can indicate the presence of a carcinogenic compound or its biological interactions. This is achieved by assaying levels of the chemical, a metabolite or a reaction product in blood, urine, saliva, cerebrospinal fluid, or other biological samples. In this way, exposure biomarkers can provide direct evidence of human exposure to a carcinogen as well as the internal dose. It is
important to take into consideration any factors that may impact on target organ concentrations, such as individual phenotype. Unless a relationship can be established between biomarker levels and external and internal dose, data from exposure biomarkers cannot be used to back-calculate the initial dose. This is because there may be interfering factors to be taken into account, for example, that the presence of a biomarker associated with one chemical may also be attributable to unrelated chemicals, or the background exposure to the chemical in question may be at a level where the metabolism is saturated and as a result the biomarker does not reflect exposure.

12. Biomarkers such as adducts are important in understanding the kinetics and potential biological interactions of a chemical, for example if it is capable of interacting with DNA. In general, biomarkers of exposure are short-lived and provide only short- to medium-term indications of internal exposure.

13. Biomonitoring, the direct measurement of a putative carcinogen or its metabolites in biological samples, has been widely used within the risk assessment process. Some examples of biomarkers of internal exposure are provided in (Angerer et al., 2007). Biomarkers of exposure can be used in animal studies to provide important information which can contribute to carcinogenic MOA investigations. For example, investigations of the carcinogenic potential of acrylamide utilise DNA and haemoglobin (Hb) adduct data (Hogervorst et al., 2010; Klaunig and Kamendulis, 2005).

**DNA adducts**

14. DNA adducts, DNA covalently bound to a chemical moiety, characterise the first stage of DNA damage and provide a marker of exposure to reactive chemicals or their metabolites. The presence of DNA adducts may demonstrate systemic exposure to specific target tissues. Their measurement can be used in human biomonitoring studies investigating environmental exposures to chemicals. DNA adducts can be measured in peripheral blood lymphocytes (PBLs), exfoliated cells, such as from the urothelium or buccal mucosa, and in tissue biopsy samples.

15. DNA adducts are commonly used as biomarkers of exposure when investigating exposure to polycyclic aromatic hydrocarbons (PAHs) from sources such as smoking (Phillips, 2005; Veglia et al., 2003), environmental pollution (Farmer et al., 2003; Singh et al., 2007) or occupational exposure (Lee et al., 2003; Taioli et al., 2007). The epidemiological link between aflatoxin B1 exposure and hepatocellular carcinoma development is strongly supported by investigations using DNA adducts as biomarkers of exposure (Rundle, 2006; Wogan et al., 2011). In addition, aflatoxin biomarkers have sufficient predictive value for cancer outcome to be used as short-term indicators for intervention trials (Kensler et al., 2003). Exposure to acrylamide is strongly associated with the production of DNA adducts in vitro and in animals but the correlation is less clear in humans (Xu et al., 2014, Li et al., 2016). The mode of action of aristolochic acid, a naturally occurring component of *Aristolochia* species associated with nephropathy and urothelial cancer, has been...
investigated using DNA adducts and specific DNA adducts have been identified as a biomarker in an exposed population (Jadot et al., 2017).

16. The biological significance of DNA adducts has been considered by ECETOC and ILSI/HESI workshops (Pottenger et al., 2009; Sander et al., 2005). Both reached the general consensus that DNA adducts had an important role in the risk assessment process and in establishing mode of carcinogenic action. However, adducts vary greatly in their mutagenic potency and it is not possible to establish a generic level below which there is no adverse biological response. Understanding the role of processes such as DNA repair, cell turnover and death is critical to establishing the significance of adducts in the generation of mutagenic lesions and the subsequent development of a tumour. Accordingly, association of an adduct with a disease does not automatically indicate causality, although there is considerable evidence indicating that they can inform epidemiological investigations with regard to causation. It has also been proposed that DNA adducts can be useful biomarkers of cumulative exposure, representing cumulative unrepaired DNA damage (Vineis and Perera, 2000).

17. Frameworks and guidance have been developed by ILSI-HESI workgroups with a view to standardising methodological approaches and for data presentation and interpretation. An organisational approach for the assessment of DNA adduct data outlines how information which defines and characterizes the DNA adduct (e.g. type of adduct, frequency, persistence, type of repair process) should be integrated with other relevant data, such as dosimetry, toxicity, toxicokinetics, genotoxicity, and tumour incidence, to inform on the chemical MOA. DNA adducts are considered biomarkers of exposure, whereas gene mutations and chromosomal alterations represent biomarkers of early biological effects but are also potential bio-indicators of the carcinogenic process (Jarabek et al., 2009). DNA adduct data are most effectively utilised when viewed in the context of other information within the risk assessment framework.

18. Methods of identification and quantitation of DNA damage include $^{32}$P-postlabelling, mass spectrometry, immunoassay and fluorescence detection (Himmelstein et al., 2009). Himmelstein et al (2009) provide comprehensive discussions of the collection, processing and storage of biological samples for subsequent analysis of biomarkers of DNA damage. Attention should be given to validation at all stages of development, and this should address analytical and biological aspects of the methods including the half-life of the adduct under investigation.

Protein (Haemoglobin or Albumin) adducts

19. Adducts of chemicals with proteins such as Hb and albumin can also be used as biomarkers of exposure to carcinogens. Occupational exposure to 1,3-butadiene and styrene have been effectively investigated using Hb-adduct methodology (Vacek et al., 2010; Boysen et al., 2012; Ogawa et al., 2006). Acrylamide exposure in humans has been successfully monitored by measuring Hb adducts of acrylamide
itself or its metabolite glycidamide (Vikstrom et al., 2012). Similarly, albumin adducts of aflatoxin have been detected in exposed populations (McCoy et al., 2008) and biomonitoring of arylamines and nitroarenes utilises albumin adducts (Sabbionu and Turesky, 2017).

**Biomarkers of Effect**

20. Biomarkers of a key event implicated in a carcinogenic mode of action may be used to characterise the hazard. With regard to carcinogenicity, the most commonly studied biomarkers of effect measure genotoxicity endpoints such as chromosomal changes (Albertini et al., 2000; Bonassi et al., 2005). It is important to recognise that, in some instances, these biomarkers of effect may only be indicative of immediate alterations and may not represent injury resulting in actual impairment of health or disease. Biomarkers of effect are frequently not specific to a given exposure or a specific agent. The relationship between exposure (acute, subacute, or chronic), the biomarker of effect, and carcinogenic event must be established in order to determine validity. For non-genotoxic carcinogens, biomarkers measuring key events in the respective mode of action can be of value. Examples include changes in hormone levels, such as elevated thyroid stimulating hormone seen in rats given thiazopyr (Dellarco et al., 2006) and evidence of cell-specific toxicity, such as the peroxisome proliferation induced by a variety of chemicals such as phthalate esters which are carcinogenic in the rodent liver (Holsapple et al., 2006; Klaunig et al., 2003).

**Genotoxicity Biomarkers**

21. Cytogenetic endpoints such as micronuclei (MN) and chromosome aberrations (CA) are considered to be biomarkers of early carcinogenic (genotoxic) effect and are thought to be predictive for cancer risk in humans (Bonassi et al., 2011; Fenech et al., 1999). Sampling of blood and the preparation and analysis of peripheral blood lymphocytes (PBLs) for MN or CA are techniques often used in occupational and environmental biomonitoring studies (Bonassi and Au, 2002; Bonassi et al., 2005).

22. An example of the use of genotoxicity biomarkers in risk assessment is the detailed assessment that was undertaken by the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) of studies measuring MN and CA in workers exposed to pesticides (Bull et al., 2006). Factors such as age, gender, vitamin B12 and folate status were found to impact strongly on background levels of these biomarkers and, because of this inherent variability, it was difficult to evaluate the significance of the findings (Battershill et al., 2008; Fenech and Bonassi, 2011). It was concluded that these factors need to be accounted for when designing biomonitoring studies and similar conclusions are documented in a COM statement (COM, 2006).

23. The comet assay, an assay which detects single strand breaks and alkali-labile lesions in DNA using PBLs, can also be used in investigations evaluating
populations potentially exposed to genotoxicants and has shown some promise as a biomonitoring tool (Collins et al., 2014). Although not all types of carcinogenic exposures will cause lesions in PBLs detectable as comets, the assay is considered to be a valuable method for detection of genotoxic exposure in humans. However, its value for predicting cancer is not yet known because it has not been investigated in prospective cohort studies. An understanding of the factors influencing background levels is also critical in the design of such studies and a role of genotype is also implicated in this variability (Koppen et al., 2017).

24. 8-Hydroxy-2’-deoxyguanosine (8-OHdG) is a marker of oxidative damage to DNA developed as a biomarker of biochemical effect. 8-OHdG levels can be assessed using PBLs and, as oxidised DNA repair products are excreted, they can also be assayed in biofluids such as urine (Loft et al., 2012a). 8-OHdG levels have been widely used in studies examining workers occupationally exposed to PAHs (Angerer et al., 2007; Marczynski et al., 2002). There is good evidence that increases in this biomarker correlate with exposure to potential mutagens and these increases are broadly in accordance with comet results (Loft et al., 2012b). Whilst there is good experimental evidence that 8-OH-dG has potential as a biomarker of effect, its reliability is still being evaluated and is the subject of extensive research.

25. Sister chromatid exchanges (SCE) reflect an interchange between DNA molecules at homologous loci within a replicating chromosome. The in vitro sister chromatid exchange (SCE) test in mammalian cells has been used to investigate chemicals with the potential to damage DNA. However, not all test substances that induce chromosome aberrations induce SCEs. The significance to human health is unclear as SCEs are a reflection of DNA repair by homologous recombination. The test is no longer recommended for the routine evaluation of test materials and has been superseded by other methodologies, such as the comet assay for this purpose (OECD, 2017).

26. An increased incidence of MN and DNA damage has been demonstrated in hospital personnel exposed to antineoplastic drugs (Mahmoodi et al., 2017) and a meta-analysis showed that frequencies of MN and CA in PBLs may be indicators of early genetic change in populations occupationally exposed to PAHs (Wang et al., 2012). However, evidence that genotoxicity biomarkers are indicative of cancer risk in humans is not extensive. Furthermore, the presence of genotoxicity biomarkers does not inform on the precise nature of the chemical exposure which has occurred to give rise to the measured endpoint.

Molecular Epidemiology in Cancer Risk Assessment

27. Molecular epidemiology is a term which encompasses the use of biomarkers to investigate the events and potential mechanisms which occur during the process of carcinogenicity, from initial exposure to disease (Vineis and Perera, 2007). The methods used can potentially represent biomarkers of exposure and biomarkers of effect. There have been significant developments in this field, underpinned by the improvement of genetic and molecular techniques identifying environmental and
genetic risk factors in the aetiology of cancer. There is a large body of literature which describes the development of potential new biomarkers of exposure and effect and discusses the usefulness and limitations of biomarker measurement (e.g. Ceccaroli et al, 2015).

28. Studies designed to investigate the relationship between chemical exposures and genetic changes, the ‘meet in the middle approach’, are considered a plausible and increasingly necessary progression to predict more accurately the impact of environmental exposures on cancer aetiology (Vineis and Chadeau-Hyam, 2011; Vineis and Perera, 2007). There is an expectation that an improvement of exposure assessment will greatly enhance understanding of early changes in the carcinogenic process. However, it is noteworthy that many of the techniques are still experimental and although they are useful for qualitative measurements and/or MOA investigations, it is not currently possible to provide specific guidance on their usefulness in a quantitative capacity.

**Biomarkers of Susceptibility**

29. The role of genetic polymorphisms and other factors that determine an individual’s susceptibility to cancer is becoming an increasingly widespread topic in cancer risk assessment. Individual gene polymorphisms, which may be considered to be biomarkers of susceptibility, differ for different tumour types. For example, associations between polymorphisms in genes coding for xenobiotic biotransforming enzymes such as $N$-acetyltransferase 2 (NAT2) and glutathione S-transferase M1 (GSTM1) and individual susceptibility to a number of different bladder, lung and colorectal carcinogens have been made, although the evidence is not conclusive (Agundez, 2008; Dong et al., 2008; Garcia-Closas et al., 2005; Sanderson et al., 2007). Polymorphisms in DNA repair enzymes have also been implicated as biomarkers of cancer susceptibility (Karahalil et al., 2012).

30. Genome-wide association studies (GWAS) examine common genetic variants in different individuals, principally single-nucleotide polymorphisms (SNPs), and attempt to identify variations associated with traits or diseases, including cancer. GWAS are used by epidemiologists to understand gene-environment interactions responsible for carcinogenesis (Boffetta et al., 2012; Vineis et al., 2008). Several large projects and consortia are now in progress, studying genetic variation in the aetiology of different cancers, e.g. under the International Agency for Research on Cancer (see [http://epic.iarc.fr/research/activitiesbyresearchfields/geneticepidemiology.php](http://epic.iarc.fr/research/activitiesbyresearchfields/geneticepidemiology.php), accessed 02/05/17) and the US National Cancer Institute (see [https://epi.grants.cancer.gov/gameon/](https://epi.grants.cancer.gov/gameon/), accessed 02/05/17). The Committee has considered GWAS previously and interactions between genotype and chemicals in the environment. A paper on how these data should be used in the risk assessment process was also considered. It was concluded that, whilst such data are useful, it would be difficult to use the derived information for the risk assessment of specific chemical carcinogens at the current stage of technique development without a
clearer understanding of the functional links and biological relevance of each genotype (COC, 2011).

Omics technologies

31. The development of omics technologies (genomics, proteomics, metabolomics), the investigation of gene and protein changes following chemical exposure, and its use in toxicological risk assessment has previously been reviewed in detail by the COT, COC and COM (COT, COC and COM, 2004; COT, 2012). With reference to mutagenesis, the COM has examined the literature for studies using toxicogenomic techniques which provide evidence of specific patterns of gene alterations induced following exposure to mutagenic chemicals. It was concluded that there was insufficient information to identify clearly genotoxic responses in vivo and that there was a need for more research on the application of integrated toxicogenomic approaches to evaluating changes in response to exposure to mutagens and determining carcinogenic modes of action (COT, COC and COM, 2004). The specific use of omics technologies for biomarkers of exposure or the potential for their use in examining the outcome of chemical exposures in human populations is not yet validated. Understanding and differentiating between exposures to genotoxic and non-genotoxic carcinogens will likely be facilitated by the use of omics approaches (Hochstenbach et al., 2012).

32. Metabolomics is the study of the biochemical composition of the outcome of metabolic pathways (metabolites) including those which occur after exposure to chemicals. The metabolome can be measured noninvasively by sampling body fluids such as urine. Profiles can inform on chemical exposures and the effects of those exposures and show promise in biomarker development (Chadeau-Hyam et al., 2011). Metabolomes have the potential to be used as biomarkers of exposure and effect, and to provide information on both genotoxic and non-genotoxic carcinogenic modes of action. Examples of the use of metabolomics in the assessment of cancer risk are starting to emerge (Harris et al., 2015).

33. The application of omics technologies to carcinogenicity evaluation was considered by the COC as part of its discussions on alternatives to the use of the 2-year rodent bioassay for carcinogenicity risk assessment. The Committee concluded that the further development of biomarkers is necessary, and while much information has been generated in this area, a better understanding of the key markers is required before this can progress (see COC Guidance Statement G07 Part C1).

34. The conceptual term ‘exposome’ has been coined to describe the totality of environmental exposures to chemicals and there is increasing discussion on how this can be utilised to understand disease (Peters et al., 2012; Rappaport and Smith, 2010; Wild, 2005, 2012). Some examples of approaches include omics technologies, the use of large scale prospective cohorts such as Biobank UK, and improved monitoring, for example in occupational settings or dietary intakes (Wild,

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11 At time of publication of version 1-1 of this statement, G07 Part C was not yet published
2012, Athersuch, 2016). EXPOsOMICS is a collaborative EU project using omics techniques and environmental exposure (air, water) data to study the role of the environment in human disease (Vineis et al., 2017). Exposome-Explorer (http://exposome-explorer.iarc.fr) is a database dedicated to biomarkers of exposure to environmental risk factors (Neveu et al., 2017).

35. Epigenetics, heritable changes in gene expression which are independent of changes in DNA sequence, is another rapidly growing area of investigation which is implicated in the process of carcinogenesis (Barrow and Michels, 2014). Epigenetic mechanisms include changes in DNA methylation. There is evidence that some chemical exposures result in epigenetic modifications which could impact on the induction of cancer and may act as historical biomarkers of exposure (Verma, 2015). In the near future, permanent changes in gene expression and epigenetic changes may provide new biomarkers of exposure and of effect that will have utility in longer term epidemiological studies. The possibility of use of epigenetic change as a biomarker of exposure has been explored in an ECETOC workshop on markers for improved retrospective exposure assessment. (ECETOC, 2009) and discussed at the joint COC, COM and COT meeting in October 2017 where use of epigenetics in chemical risk assessment was discussed.

36. miRNA species are another promising area for biomarker development. These short RNA species are non-protein-coding RNAs, which have a role in the regulation of translation of protein from mRNA. These species are differentially expressed in many cancer types and found in the circulation (Brase et al., 2010; Calin and Croce, 2006; Mitchell et al., 2008; Mo et al., 2012). This gives them much utility as biomarkers of effect. miRNA species are coded from regions of the genome that can be under epigenetic control and can be differentially methylated in cancer (Chuang and Jones, 2007; Li et al., 2012; Lujambio et al., 2008). This raises the possibility that epigenetic change resulting from carcinogen exposure may lead to altered miRNA expression via differential methylation and that this could be a biomarker of historical carcinogen exposure and arbiter of potential future effect (Vrijens et al., 2015). The use of non-coding RNAs as potential biomarkers in regulatory toxicology was discussed at an ECETOC workshop, during the summary of which it was noted “To make available ncRNAs as biomarkers for regulatory toxicology and RA, normal and adverse ncRNA profiles and dose-response relationships of effects should be determined, and ncRNA expression profiles should be linked to phenotypic alterations. Further, it should be determined whether ncRNA levels in specific body fluids reflect levels in specific target tissues. Even though a number of research projects demonstrated a lack of toxicologically relevant uptake and activity of ingested RNAs, bioavailability of ingested ncRNAs and potential impacts to the consuming organism may merit further investigation” (ECETOC, 2016).

37. A Biomonitoring Equivalent (BE) is 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 Tolerable Daily Intake (TDI) or
reference dose or concentration (RfD, RfC). It provides a way of interpreting biomonitoring data in the context of these values (Hays et al., 2008; LaKind et al., 2008). It is envisaged that they will be useful for understanding and prioritising risk management practices and will enable the available biomonitoring data to be utilised more fully. However, to date, there is limited information on the use of BEs for estimating chemical exposure in the context of carcinogenesis.

Summary

38. A biomarker, in the context of chemical carcinogenesis, is defined as an observable change related to a specific exposure or effect.

39. In cancer risk assessment, biomarkers can be utilised for hazard identification and characterisation and for exposure assessment.

40. The relationship between the biomarker and the carcinogenic response should be established.

41. Biomonitoring studies should fulfil pre-defined criteria and biomarkers should be appropriately characterised and validated. Particular attention should be given to ascertaining the stability and half-life of the biomarker and how these impact on the interpretation of epidemiological data.

42. Biomarkers of exposure include DNA and protein adducts, MN and CA. Biomarkers of effect include genotoxicity biomarkers such as MN and CA, and the indicator of oxidative damage, 8-OHdG.

43. The Committee maintains an on-going awareness of the development of newer techniques including molecular epidemiology methods, omics technologies and the emergence of the exposome. However, many of the techniques are still experimental and are useful only for deriving qualitative measurements or information contributing to MOA investigations. It is not currently possible to provide specific guidance on their use in a quantitative capacity.

44. The Committee continues to evaluate the usefulness of the entire spectrum of biomarker techniques including the applicability and interpretation of well-established methods.

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References


