CC/2017/04

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Draft updated General Introduction to G07 Alternatives to the 2-year Bioassay

Attached is a draft updated copy of the General Introduction to guidance statement G07 Alternatives to the 2-year bioassay, which incorporates more detail on sections c and d which are currently in draft as tracked changes. It is intended to publish the full version of G07 incorporating parts c and d and this updated introduction when both the draft sections have been agreed by the Committee.

Members are invited to comment on the amendments made to the introduction.

Imperial College Toxicology Unit/Secretariat
March 2017

Committee on CARCINOGENICITY

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

Statement COC/G07 - Version 1.1 draft

Alternatives to the 2-year Bioassay

DRAFT

https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc

COC Secretariat

c/o Public Health England

Centre for Radiation, Chemical and Environmental Hazards

Chilton, Didcot, Oxfordshire OX11 0RQ

© Crown copyright 2017

Deleted: 2016

You may re-use this information (excluding logos) free of charge in any format or medium, under the terms of the Open Government Licence v3.0. To view this licence, visit OGL or email psi@nationalarchives.gsi.gov.uk. Where we have identified any third party copyright information you will need to obtain permission from the copyright holders concerned. Any enquiries regarding this publication should be sent to COC@phe.gov.uk.

Committee on CARCINOGENICITY

COC/G07 – Version 1.1 draft

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Alternatives to the 2-year Bioassay

General Introduction

1. This guidance statement comprises four parts, which together provide an overview of approaches that have been proposed as alternatives to the 2-year rodent bioassay for carcinogen risk assessment:

   a. *in vivo* assays
   b. cell transformation assays
   c. emerging technologies: omics and high-throughput screening
   d. alternative testing strategies for carcinogens incorporating results from short-term tests

It is part of the Committee of Carcinogenicity (COC) guidance statement series which provides the Committee's views on all aspects of carcinogen risk assessment. It should be read in conjunction with G03 Hazard Identification and Characterisation: Conduct and Interpretation of Animal Carcinogenicity Studies.

2. The conduct of 2-year bioassays in two species, usually rat and mouse, has underpinned carcinogenicity risk assessment since the standard assay was developed in the 1960s (Cohen, 2010a,b). The objective of these long-term studies is to observe animals for the development of neoplastic lesions following exposure to a test substance for a major part of their life-span. The studies are usually designed to conform to closely defined test protocols and procedures (OECD GL 451 and 453, see Guidance Statement G03).

3. A significant body of data is available, particularly from the US National Toxicology Program (NTP), which has evaluated a large number of known carcinogens using the standard 2-year bioassay. Carcinogenicity testing strategies were developed taking into consideration the assumptions that, biologically, humans and animals are intrinsically similar and that carcinogenesis is a multistage process (Boobis et al., 2009). However, it has become evident that the conditions under which chemicals are tested are not necessarily relevant to human exposure, for example, the use of the maximum tolerated dose (MTD) and that some modes of carcinogenic action (MOA) are not relevant to human risk assessment. Furthermore, standard carcinogenicity study protocols involve the use of large numbers of animals (approximately 400-500 of each species) and, with increasing concern surrounding

Deleted: <#>developing methodologies and strategies[1] (for example toxicogenomics)¶

Deleted: paradigms[2] (for example, evaluation using histopathology and proliferative markers in sub-chronic rodent studies)

Deleted: or

unnecessary or poorly designed studies, efforts are being made to reduce animal use and to develop testing strategies that are more refined, in line with the principles of 3Rs[3].

4. The use of both rat and mouse 2-year bioassays in assessing the carcinogenic potential of chemicals has been subjected to close scrutiny. Several detailed evaluations of datasets have been undertaken with a view to assessing the utility of the mouse bioassay and the relevance of non-genotoxic, liver-only rodent carcinogens (Schach von Wittenau & Estes, 1983, cited by Alden et al., 1996; Huff et al., 1991, cited by Alden et al., 1996; Billington et al., 2010; Osimitz et al., 2013).

5. These investigations and analyses suggest that a single 2-year rodent assay is sufficient for cancer hazard identification. This view is endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which indicates that bioassay data from only one species (e.g. the rat) is required for evaluation of carcinogenic potential, when supported by appropriate mutagenicity and pharmacokinetic studies and a study from a short-term *in vivo* assay, such as a transgenic mouse model (ICH, 1998). ICH is now prospectively testing a strategy for evaluation of pharmaceuticals using a weight of evidence approach to define situations where a complete waiver of a 2-year bioassay would be justified (ICH, 2016).

6. For chemicals, some alternative strategies to the 2-year bioassay are being developed, which incorporate short-term endpoints (e.g. histopathology findings) in carcinogenicity evaluations based on tiered and weight of evidence-based approaches, focusing on human-relevant modes of action. These methods vary depending on the type of compound being evaluated and the purpose of the evaluation, and it is not yet clear whether they will be feasible for risk assessment purposes.

7. As well as alternative *in vivo* models, *in vitro* cell transformation assays have been developed as alternative methods to detect carcinogenic potential, in particular for use in testing scenarios where *in vivo* testing is not permitted (e.g. cosmetics testing). Recent developments in 'omics' technologies such as genomics, proteomics and metabolomics, enable detailed examination of chemically induced changes in the regulation of genes, proteins and metabolite profiles, respectively. These methods are considered useful in providing insight into the mode and mechanism of action of chemical carcinogens and as a prioritising and/or predictive tool for carcinogen identification. In parallel, high-throughput screening methods are being developed to screen large numbers of chemicals over a wide range of assay conditions.

[3] https://www.nc3rs.org.uk/the-3rs

Deleted: more refined

Deleted:

Deleted: . In an assessment by

Deleted: (

Deleted:) (

Deleted:), of 273 chemicals tested in both rats and mice, 206 were positive in both species whilst only 9 were positive in the mouse, and negative or inconclusive in the rat. Similarly, in an assessment by

Deleted: (

Deleted:) (

Deleted:), 18 of 313 chemicals tested in both rats and mice in NTP studies were positive only in the mouse (i.e. 5.7%). Of 202 pesticides evaluated in the European Union, only 3 produced tumours only in mice (

Deleted:). In a further review of data from 710 chemicals which had been tested in both the mouse and rat bioassays, only 3 compounds were identified as unequivocally non-genotoxic, mouse carcinogens in organs other than the liver. Mouse only, non-genotoxic liver carcinogenicity has been considered an unreliable indicator of human carcinogenic potential for some years (

Deleted: two

Deleted:)

Deleted: Furthermore, recent

Deleted: -

Deleted: They

Deleted: the effects

Deleted: , including carcinogenicity risk assessment

8. The following parts of this Guidance Document present the Committee's opinions and views on the approaches with the potential to be used as alternatives to the 2-year rodent bioassay in a carcinogenicity testing strategy.