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Review

Approaches for identifying germ cell mutagens: Report of the 2013 IWGT workshop on germ cell assays☆

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ABSTRACT

This workshop reviewed the current science to inform and recommend the best evidence-based approaches on the use of germ cell genotoxicity tests. The workshop questions and key outcomes were as follows. (1) Do genotoxicity and mutagenicity assays in somatic cells predict germ cell effects? Limited data suggest that somatic cell tests detect most germ cell mutagens, but there are strong concerns that dictate caution in drawing conclusions. (2) Should germ cell tests be done, and when? If there is evidence that a chemical or its metabolite(s) will not reach target germ cells or gonadal tissue, it is not necessary to conduct germ cell tests, notwithstanding somatic outcomes. However, it was recommended that negative somatic cell mutagens with clear evidence for gonadal exposure and evidence of toxicity in germ cells could be considered for germ cell mutagenicity testing. For somatic mutagens that are known to reach the gonadal compartments and expose germ cells, the chemical could be assumed to be a germ cell mutagen without further testing. Nevertheless, germ cell mutagenicity testing would be needed for quantitative risk assessment. (3) What new assays should be implemented and how? There is an immediate need for research on the application of whole genome sequencing in heritable mutation analysis in humans and animals, and integration of germ cell assays with somatic cell genotoxicity tests. Focus should be on environmental exposures that can cause de novo mutations, particularly newly recognized types of genomic changes. Mutational events, which may occur by exposure of germ cells during embryonic development, should also be investigated. Finally, where there are indications of germ cell toxicity in repeat dose or reproductive toxicology tests, consideration should be given to leveraging those studies to inform of possible germ cell genotoxicity.

☆ Where applicable, this manuscript has been reviewed by the institutions of those authors and approved for publication. The opinions and conclusions expressed in this article are the views of the authors and do not necessarily reflect those of their institutions. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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Contents

1. Introduction

Fifteen internationally recognized germ cell genetic and reproductive toxicology experts from government, industry, and academia, gathered in Foz do Iguacu, Brazil (October 31–November 1, 2013) for an International Workshops on Genotoxicity Testing (IWGT) meeting on advancing the science and regulatory approaches used to assess mutagenic hazards to germ cells. The overarching mandate of this workshop was the following: (1) review the current science; (2) achieve scientific consensus on issues surrounding the use of germ cell genotoxicity tests in regulatory assessments; and (3) inform and recommend the best evidence-based approaches and future prospects in this field. Discussions and presentations centered on the following topics that provided a basis for achieving consensus:

- current assays used to assess germ cell mutation;
- regulatory requirements of different countries and international organizations for germ cell tests;
- reproductive toxicology assays that can be leveraged for the assessment of heritable effects;
- assays in need of further development or validation;
- new technologies and approaches;
- the "blood-testis barrier" and pharmacokinetics in male germ cell toxicity/genotoxicity;
- endpoints most relevant to human genetic risk.

Directed discussions were held on the following key workshop questions.

(1) Do genotoxicity and mutagenicity assays in somatic cells predict germ cell effects? (2) Should germ cell tests be done, and when?

(3) What new assays should be implemented and how?

The workshop resulted in recommendations addressing each of these questions, with an emphasis on the need to develop improved methods for germ cell testing, including those that can be integrated with existing genetic and reproductive toxicology tests.

2. Background

Early genetic toxicology focused almost exclusively on heritable genetic effects. However, in 1973 Dr. Bruce Ames' seminal paper [1] that introduced the Salmonella bacterial mutation assay (Ames test), and other developments, changed the focus of genetic toxicology from germ cells to somatic cells and cancer. The premise that the majority of carcinogens were somatic cell mutagens and could be readily detected with short-term assays resulted in a nearly complete shift in focus from heritable genetic hazards to somatic cell effects. Though, to date, no human germ cell mutagen has definitively been identified, nearly 50 rodent germ cell mutagens are known [2], and the consequences of heritable mutations remain of concern.

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