VII G. Heritable and Somatic Genetic Toxicity

This chapter discusses FDA's interest in direct food additives and color additives used in foods that can cause both heritable and somatic genetic toxicity. While the FDA currently neither recommends specific tests to determine somatic and heritable genetic toxicity, nor regulates food and color additives used in food on the basis of such activities, the Agency has an heightened interest in this area.

1. Rationale for Testing for Heritable and Somatic Genetic Toxicity

Heritable genetic toxicity is chemically-induced damage to the DNA of male and female germ-line cells that is not correctly repaired, so that the damaged gene(s) can be inherited. The consequences of this genetic toxicity has been well documented, and a number of different genetic diseases have been characterized. Somatic genetic toxicity is chemically-induced damage to the DNA of dividing and non-dividing somatic cells (*i.e.* non-germ-line cells). The consequence of somatic genetic toxicity is that chemicals may alter gene functions in rapidly dividing somatic cells (*e.g.* intestinal lining and bone marrow) and in quiescent cells which may be forced to replicate in response to a regenerative or mitogenic stimulus (*e.g.* G_oG_1 peripheral lymphocytes). Genetic damage to these cells can lead to cancer and alteration of critical cellular functions (*e.g.* altered hormone and receptor site functions).

2. Rationale for Selecting a Specific Test Battery

Currently the Agency recommends the use of a battery of genetic toxicity tests (see **Chapter IV C 1 c**) for all chemicals that are direct food additives or color additives used in foods, including chemicals with structures assigned to all three structure categories (see **Chapter III B 2**), as well as chemicals associated with Concern Levels I, II, and III (see **Figure 4** in **Chapter III B 1**). These tests are recommended to evaluate the genetic toxicity of chemicals in order to identify those chemicals that may be direct acting carcinogens (see **Chapter IV C 1**).

Short-term tests for genetic toxicity can also be conducted to evaluate the effects of chemicals on the genetic material of both somatic and germ-line cells, and the tests used for these purposes can overlap those used for predicting carcinogenicity. For example, the data obtained from the *Salmonella typhimurium* reverse mutation assay is not only useful in predicting the potential carcinogenicity of test substances,[1,2,3] but it is also an important means of determining whether a chemical has the potential to damage the genetic material in both germ-line and somatic cells. Although FDA considers the information obtained from the test battery recommended in **Chapter IV C 1** to be useful in assessing a chemical's potential to cause heritable and somatic genetic toxicity, the scientific community has not yet reached a consensus that these indicators are reasonably predictive of human responses.

While FDA does not recommend a unique battery of tests for determining heritable and somatic genetic toxicity, the Agency recognizes that certain types of tests may be useful for this purpose.

Historically, gene mutations in germ line cells have been detected using *in vivo* tests such as the sex-linked recessive lethal assay in *Drosophila melanogaster* and rodents. [4,5,6] Unfortunately, the standard classical assay procedures are not completely satisfactory; each of these tests has one or more of the following limitations:

- standard procedures have a very low sensitivity for detecting known mutagenic chemicals, and the assays fail to detect dose-related increases in chemical activities;

- standard protocols have many deficiencies (*e.g.* they frequently lack concurrent positive controls, multiple test chemical doses are rarely used, *etc.*);

- standard protocols for heritable genetic toxicity cannot simultaneously measure somatic cell toxicity in the same animals; and

- standard methods require large numbers of animals and are very time consuming and expensive.

Thus, two groups of tests may provide a sensitive method for detecting heritable and somatic cell genetic toxicity. First, a battery of tests for germ-line and somatic cell genetic toxicity should include the same short-term genetic toxicity tests used to predict potential carcinogenicity {*e.g. Salmonella typhimurium* reverse mutation assay, *in vitro* ML mutation assay and an *in vivo* cytogenetics assay (see **Chapter IV C 1**)}. Second, a battery of tests for germ-line and somatic cell genetic toxicity also should include the use of transgenic mice. The Agency recognizes that current genetic toxicity tests using transgenic animals do not directly demonstrate heritable genetic toxicity effects; however, chemical-induced genetic toxicity to germ cells demonstrates the potential for this to occur. Since research with several different experimental rodent models has been progressing rapidly, and a variety of transgenic rodents are now commercially available, it may be possible in the future to simultaneously assess chemically-induced genetic damage to germ line cells and to a variety of somatic tissues. The transgenic test system should have several advantages over classical tests for heritable genetic toxicity:

- the investigator can easily manipulate the treatment conditions so that tissue-specific toxicological effects can be compared for different assay protocols;

- the test requires relatively few animals (*i.e.* 2 or 3 animals per treatment group); and

- the test is relatively inexpensive and can be performed in a matter of days.

FDA continues to encourage the scientific community to develop sensitive assays for detecting germ-line and somatic cell genetic toxicity.

References

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