Chapter V

Additional Recommended Studies

A. Introduction

The Agency recognizes that information about metabolism and pharmacokinetics, neurotoxicity, and immunotoxicity are significant endpoints in assessing the safety of direct food additives and color additives used in food. Recommended strategies for improving the ability to determine metabolism and pharmacokinetics and the neurotoxic and immunotoxic potentials of test substances are described in **Chapters V B**, **C**, and **D**, respectively. Because this chapter addresses toxicity studies that are recommended for the first time by FDA for assessing the safety of direct food additives and color additives used in food (see **Figure 4**, **Chapter III C 1**), they are discussed in greater detail than other recommended toxicity studies (see **Chapter IV C**).

1. Metabolism and Pharmacokinetics

FDA believes that data from studies on the adsorption, distribution, metabolism, and excretion of a chemical can provide insight into mechanisms of toxicity and are essential in the design and evaluation of results from other toxicity studies. Such data should be provided for all direct food additives and color additives used in food that are assigned to Concern Levels II or III. Recommendations for obtaining data on the metabolism and pharmacokinetics of these substances are presented in this document. In general, the Agency recommends that this information be obtained before subchronic and chronic toxicity tests are begun.

2. Neurotoxicity

It is recommended that the assessment of neurotoxic potential be carried out according to a process of tiered testing progressing from the identification of chemicals associated with neurotoxic effects (**screening**), through a characterization of the scope of nervous system involvement (**characterization of effects**), to the determination of dose response kinetics which includes the definition of the no-observed adverse effect level (**dose-response**). Screening for neurotoxic effects, which is considered to be one of the most critical steps in this tiered process, should be routinely and systematically carried out in short-term (see **Chapter IV C 3**), subchronic (see **Chapter IV C 4**), and reproductive and developmental toxicity (see **Chapter IV C 9**) studies. The neurotoxicity screen should include a specific histopathological examination of representative tissue samples of all major areas of the brain, spinal cord, and peripheral nervous system in conjunction with a functional evaluation battery of quantifiable observations and manipulative tests selected to detect signs of neurological, behavioral, and physiological dysfunctions. References to published literature that can guide the petitioner in selecting an appropriate neurotoxicity screen are included.

Study reports should include an integrated assessment of the potential for the test chemical to adversely affect the structural or functional integrity of the nervous system. This assessment should include results of the neurotoxicity screen and other toxicology data, as appropriate. Based on the assessment, an explicit statement should be made as to whether or not the test chemical represents a potential neurotoxic hazard which requires special testing. Recommendations about further neurotoxicity testing, if the results of the initial screens indicate the need for such testing, are included. However we urge petitioners to consult with Center scientists before undertaking additional neurotoxicity tests.

3. Immunotoxicity

An immunotoxicity screen should be routinely carried out in short-term (see **Chapter IV C 3**), subchronic (see **Chapter IV C 4**), and reproductive and developmental toxicity studies (see **Chapter IV C 9**). This screen consists of primary indicators of immunotoxicity described in **Chapter V D 3**; these indicators are a set of hematological, serum protein, histopathological, and body and organ weight endpoints that are routinely evaluated in standard toxicity tests.

Study reports should include an integrated assessment of the potential for the test chemical to adversely affect the immune system. This assessment should be based on results of the immunotoxicity screen (primary indicators of immunotoxicity) and other toxicology data, as appropriate. Based on the results of this assessment, an explicit statement should be made as to whether or not the test chemical represents a potential immunotoxic hazard which requires additional immunotoxicity testing (see **Chapter V D 4** and **5**).

If results of the immunotoxicity screen indicate the need for further testing, information that will help the petitioner choose additional immunotoxicity tests is provided. However, we urge petitioners to consult with Center scientists before undertaking additional immunotoxicity tests.