参考資料１０

Guidance for Industry

Summary Table of Recommended Toxicological Testing for Additives Used in Food

Comments and suggestions regarding this document may be submitted at any time. Submit comments to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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Additional copies are available from:
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http://www.cfsan.fda.gov/guidance.html

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
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Guidance for Industry[1]

Summary Table of Recommended Toxicological Testing for Additives Used in Food

I. Introduction

The purpose of this document is to provide a brief summary of recommendations for the minimum toxicity tests to be performed for safety evaluation of direct food additives and color additives used in food based on their levels of concern. Information in this document can be used as general guidance for the determination of concern levels, as well as the extent and types of toxicity testing for direct food additives and color additives used in food. For specific questions you are encouraged to discuss them with the appropriate regulatory staff in the Division of Petition Review at the Office of Food Additive Safety. This document, reformatted in 2006, summarizes information published in the 1993 draft Redbook II. It supersedes previous versions released in 1983 and 1997. No substantive changes have been made.

II. Background

Safety evaluation for a direct food additive or color additive used in food involves assigning the additive to a Concern Level (i.e., low (I), intermediate (II) or high (III)) based on information on the additive's toxicological potential predicted from its chemical structure (i.e., low (A), intermediate (B), or high (C)) and an estimation of cumulative human exposure. For additional details, see chapter III from the draft 1993 Redbook II. Frequently, exposure information has more weight than structure alert information in assigning additives to a Concern Level. If available, other information may be considered when setting the concern level for a food or color additive, and final safety decisions are made on a case-by-case basis [2].

For information on the recommendations for the minimum toxicity tests to be performed for safety evaluation of indirect food additives, which are now referred to as food contact substances, see Guidance for Industry: Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations.

III. Recommended Toxicological Testing Summary Table for Additives Used in Food

Toxicity Tests[3]	Concern Levels		
	Low (I)	Intermediate (II)	High (III)
Genetic toxicity tests	X	X	X
Short-term toxicity studies with rodents	X[c]	X[a,c]	X[a,c]
Subchronic toxicity studies with rodents		X[c]	X[a,c]
Subchronic toxicity studies with non-rodents		X[c]	X[a,c]
One-year toxicity studies with non-rodents			X[c]
Chronic toxicity or Combined chronic toxicity/carcinogenicity studies with rodents (available in PDF from 1993 Draft Redbook II)			X[c]
Carcinogenicity studies with rodents including ***in utero*** **exposure phase** (available in PDF from 1993 Draft Redbook II)			X
Reproduction studies		X[c]	X[c]
Developmental toxicity studies		X[b,c]	X[b,c]
Metabolism and Pharmacokinetic studies (available in PDF from 1993 Draft Redbook II)		X[b]	X[b]
Human studies (available in PDF from 1993 Draft Redbook II) incuding Epidemiology Studies			X[b]

[a] **If needed as preliminary to further study.**

[b] **If indicated by available data or information**

[c] **Including screens for neurotoxicity and immunotoxicity (available in PDF from 1993 Draft Redbook II).**

IV. Concern Levels (CL) as Related to Human Exposure and Chemical Structure

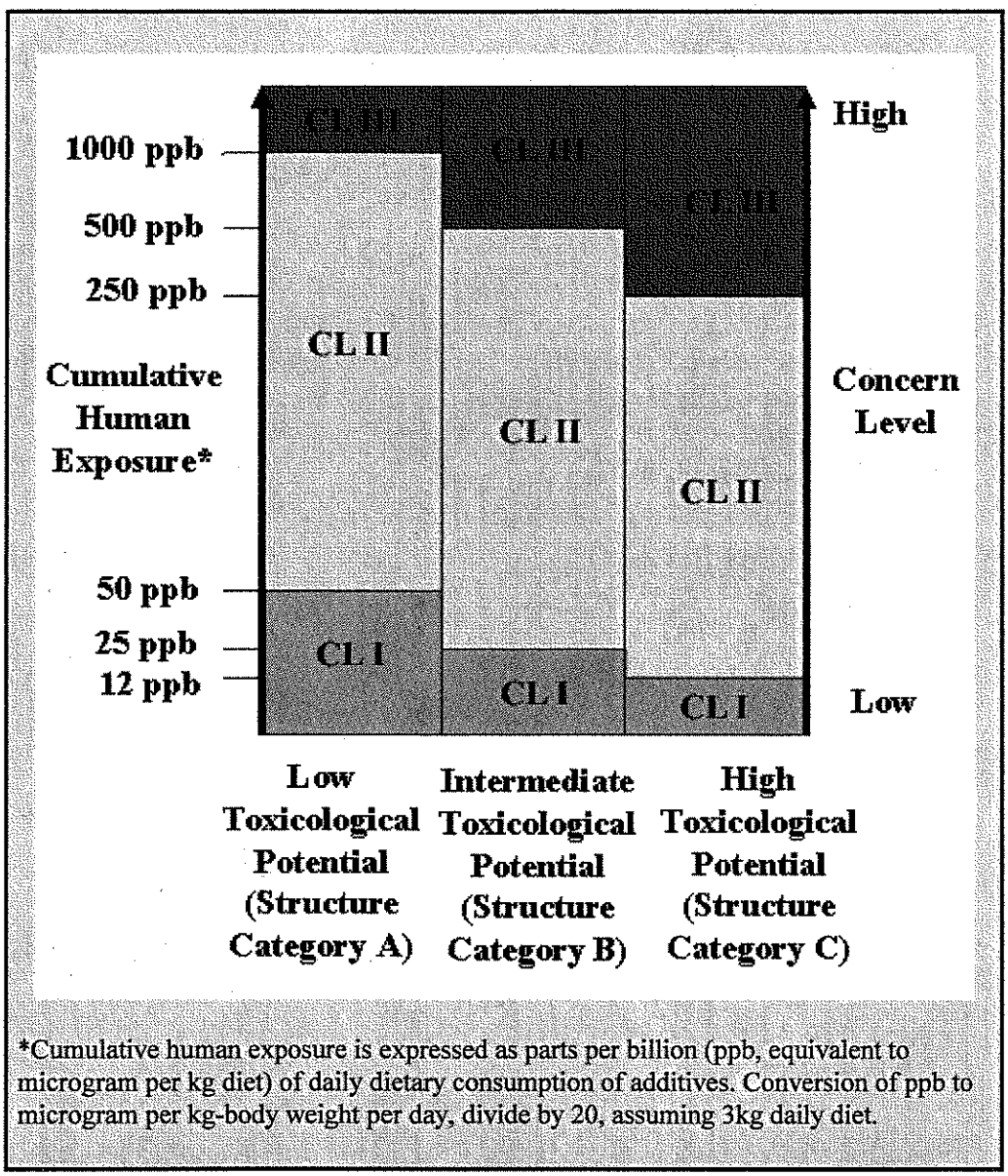

Diagram Description

This diagram depicts the minimum Concern Level that would be assigned to a direct food additive or color additive to be used in food based on the substance's estimated human exposure from the proposed use and potential toxicity based on structural similarity to known toxicants in the absence of toxicological information of an additive. Based on information about the additive's structure, the additive will be placed in one of three broad categories: Category A is for low toxicological potential, Category B is for intermediate potential, and Category C for high toxicological potential. Within each structure category (A, B, and C), estimated human exposure will determine the initial Concern Level to which the additive is assigned. Recommended breakpoints of exposure have been identified in this diagram that define the concern level for each structure. The Concern Level translates to the minimum set of recommended toxicity tests needed to evaluate the toxicological safety of the new or expanded use of the additive. Category

A structures with cumulative human exposure from 0 to 50 ppb fall into Concern Level (CL) I , CL II from 50 ppb to 1000 ppb, and CL III above 1000 ppb. Category B structures with cumulative human exposure from 0 to 25 ppb fall into CL I, CL II from 25 ppb to 500 ppb, and CL III above 500 ppb. Category C structures with cumulative human exposure from 0 to 12 ppb fall into CL I, CL II from 12 to 250 ppb, and CL III from 250 ppb and above.

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[1] This guidance has been prepared by the Division of Petition Review in the Office of Food Additive Safety, Center for Food Safety and Applied Nutrition (CFSAN) at the U.S. Food and Drug Administration.

[2] Minimum toxicological testing recommended to support the safety of a novel additive might include studies generally recommended for a Concern Level III additive, irrespective of its chemical structure and exposure. Additionally, toxicological testing may be needed for metabolites or degradation products, as well as for possible impurities, of an additive to establish safety of these components.

[3]References to current guidelines on these toxicological studies are either hyperlinked to relevant final chapters in Redbook 2000, or chapters published in the draft 1993 Redbook II.

This document supersedes Toxicological Testing of Food Additives (1983; updated 1997)
