FINAL
STATEMENT OF REASONS
22 CALIFORNIA CODE OF REGULATIONS DIVISION 2

Sections 12701, et seq. - No Significant Risk Levels
Sections 12801, et seq. - No Observable Effect Levels

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Saf. Code, § 25249.5 et seq.) (hereinafter the "Act") was adopted as an initiative statute at a general election on November 4, 1986. The Act prohibits any person in the course of doing business from knowingly discharging or releasing a chemical known to the state to cause cancer or reproductive toxicity into water or onto or into land where such chemical passes or probably will pass into a source of drinking water. (Health & Saf. Code, § 25249.5.) It further prohibits such persons from knowingly and intentionally exposing any individual to such a chemical without first giving a clear and reasonable warning. (Health & Saf. Code, § 25249.6.)

The Act also creates limited exceptions to these prohibitions. Section 25249.9 provides that section 25249.5 does not apply where a discharge or release complies with all other legal requirements and does not cause "any significant amount" of the chemical to enter any source of drinking water. The term "significant amount" is defined in section 25249.11, subsection (c) as any detectable amount except an amount which, pursuant to section 25249.10, subsection (c), poses "no significant risk assuming lifetime exposure at the level in question" for substances known to the state to cause cancer, or would produce "no observable effect assuming exposure at one thousand (1,000) times the level in question" for substances known to the state to cause reproductive toxicity. Section 25249.10, subsection (c) makes the "no significant risk" and "no observable effect" exceptions apply to the prohibition against exposure without warning.

Health and Safety Code section 25249.12 authorizes agencies designated to implement the Act to adopt regulations as necessary to conform with and implement the provisions of the Act and to further its purpose. The Health and Welfare Agency ("Agency") has been designated the lead agency for the implementation of the Act.

Procedural Background

Effective February 27, 1988, the Agency adopted Articles 7 and 8 of Chapter 3 of Division 2 of Title 22 of the California Code of Regulations to implement the no significant risk and no observable effect exemptions of the Act. Pursuant to Government Code section 11346.1, those emergency regulations were readopted on a number of occasions so as to remain in effect.

On June 10, 1988, the Agency issued a notice of emergency rulemaking advising that the Agency intended to adopt permanently Articles 7 and 8 of Title 22 of the California Code of Regulations. (See Register 88, No. 24-2, pp. 2020-2024.) Notices were also issued that the Agency intended to adopt or amend five other regulations implementing the Act. Pursuant to such notices a public hearing was held on July 29, 1988, to receive public comments on the proposed regulations, including Articles 7 and 8 (hereinafter the "July 29 proposal"). Out of forty-eight pieces of correspondence received commenting on the regulations and nine additional documents submitted at the hearing, thirty-nine (39) contained comments regarding the July 29 proposal.

On October 11, 1988, at the same time it readopted Articles 7 and 8 for the second time, the Agency issued a notice of emergency rulemaking adopting amendments to sections 12703, 12707 and 12711 of Article 7. On December 15, 1988, the Agency issued a notice of emergency rulemaking adopting further amendments to section 12711 of Article 7.

On March 29, 1989, the Agency issued a Notice of Public Availability of Changes to Proposed Regulations Regarding the Safe Drinking Water and Toxic Enforcement Act of 1986 (hereinafter the "March 29 proposal"). The notice afforded interested parties the opportunity to provide to the Agency their post-hearing comments on proposed modifications to the July 29 proposal. These proposed modifications included the amendments to sections 12703, 12707 and 12711 adopted on an emergency basis on October 11 and December 15, 1988, and amendments made in response to public comment on the July 29 proposal. The comment period for the March 29 proposal closed April 13, 1989. Twelve (12) pieces of post-hearing correspondence were received, along with supporting documents.

Purpose of Final Statement of Reasons

This final statement of reasons sets forth the reasons for the final language adopted by the Agency for Articles 7 and 8, and responds to the objections and recommendations submitted regarding those articles as originally proposed in the July 29 proposal and modified by the March 29 proposal. Government Code section 11346.7, subsection (b)(3) requires that the final statement of reasons submitted with an amended or adopted regulation contain a summary of each objection or recommendation made regarding the adoption or amendment, together with an explanation of how the proposed action has been changed to accommodate each objection or recommendation, or the reasons for making no change. It specifically provides that this requirement applies only to objections or recommendations specifically directed at the Agency's proposed action or to the procedures followed by the Agency in proposing or adopting the action.

Many parties included in their written or oral comments remarks observations about these regulations or other regulations which

do not constitute an objection or recommendation directed at the proposed action or the procedures followed. Also, many parties offered their interpretation of the intent or meaning of the proposed regulations or other regulations, sometimes in connection with their support of or decision not to object to the July 29 proposal or March 29 proposal. Again, this does not constitute an objection or recommendation directed at the proposed action or the procedures followed. Accordingly, the Agency is not obligated under Government Code section 11346.7 to respond to such remarks in this final statement of reasons. Since the Agency is constrained by limitations upon its time and resources, and is not obligated by law to respond to such remarks, the Agency has not responded to these remarks in this final statement of reasons. The absence of response in this final statement of reasons to such remarks should not be construed to mean that the lead agency agrees with them.

Specific Findings

Throughout the adoption process of this regulation, the Agency has considered the alternatives available to determine which would be more effective in carrying out the purpose for which the regulations were proposed, or would be as effective and less burdensome to affected private persons than the proposed regulations. The Agency has determined that no alternative considered would be more effective than, or as effective and less burdensome to affected persons than, the adopted regulation.

The Agency has determined that the regulation imposes no mandate on local agencies or school districts.

Rulemaking File

The rulemaking file submitted with the final regulation and this final statement of reasons is the complete rulemaking file for Articles 7 and 8. However, because regulations other than Articles 7 and 8 were also the topic of the public hearing on July 29, 1988, the rulemaking file contains some material not relevant to Articles 7 and 8. This final statement of reasons cites only the relevant material. Comments regarding the regulations other than Articles 7 and 8 discussed at the July 29, 1988, hearing have been or will be discussed in separate final statements of reason.

Necessity for Adoption of Regulations

The Agency has determined that the adoption of these regulations is necessary. The Act exempts discharges, releases and exposures which, making certain assumptions, pose no significant risk of cancer or would produce no observable reproductive effect. The Act specifies that any claim of exemption under Health and Safety Code section 25249.10, subsection (c) must be based upon evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the substance as a chemical known to the state to cause cancer or

reproductive toxicity. However, the Act does not further clarify when a chemical risk is not significant, specify levels of chemical exposure posing no significant risk, or describe methods for calculating those levels. Similarly, the Act does not specify levels of exposure to reproductive toxins which have no observable effect, and provides no methods for determining those levels.

There may be several ways to determine whether exposure to a chemical poses a significant risk. A history of exposure to a chemical through a particular medium without any significant adverse consequence may provide a basis for determining that there is no significant risk. Alternatively, more specific methods of quantification may be used. Specific epidemiological studies or animal bioassays quantifying the risk may have been performed and provide a basis for the determination of chemical potency. Specific exposures may be assessed to determine whether, based upon the potency of the chemical, the exposure in question presents a risk. The more specific approaches appear to provide greater certainty, and, therefore, appear to be preferable to more general approaches.

Generally, a specific analysis of whether exposure to a chemical poses a significant risk involves three elements. Data on the chemical risk are assessed to determine what amount of the chemical, usually expressed in terms of milligrams per day, provokes the biologic response of concern in humans. A particular level of human response must be determined to be "significant." This determination may be influenced by issues of policy and the methodology employed in the underlying risk assessment. Finally, the level of chemical exposure must be assessed. Under the Act, exposure assessment must be designed to anticipate what exposures will occur, since warnings must be given prior to exposure.

Similarly, a determination whether a chemical exposure would produce "no observable effect" involves several steps. Again, the chemical risk generally must be assessed to determine what amount of the chemical provokes the biologic response of concern in humans. An appropriate safety factor expressed as a divisor is applied to reflect the assessor's confidence in the data upon which he or she has relied. Under the Act, the safety factor is fixed at one thousand (1,000). The level of chemical exposure is then assessed to determine whether it would, as assessed, produce an observable effect or no observable effect.

There is no fixed way to perform the steps necessary to specifically determine no significant risk or no observable effect. The methods used may vary depending upon the data available, and the objectives of the risk assessor or risk manager. The purpose of these regulations is to provide some "safe harbor" levels and methodologies, and criteria for exposure assessment, which will assist persons in making certain that their discharges, releases or exposures pose no significant risk or would have no observable effect within the meaning of the Act.

The regulations are divided into two articles. Article 7, commencing at section 12701, addresses the determination of whether exposures to carcinogens listed under the Act pose no significant risk within the meaning of the Act. Article 8, commencing at section 12801, addresses the determination of whether exposure to listed reproductive toxins would produce no observable effect within the meaning of the Act.

Article 7. No Significant Risk Levels

Section 12701

Subsection (a) describes the scientific standards which must be applied to "no significant risk" determinations. It requires that such determinations be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical. In other words, a showing of no significant risk must be based upon data and protocols which are scientifically valid according to generally accepted principles, sharing a comparable degree of scientific acceptance to the data and protocols which supported the listing of the chemical. The purpose of this provision is to ensure that whatever methods are used to conduct risk and exposure assessments conform to a high standard of scientific validity as required by the Act.

One commentator recommended that data to be used by the Agency in a risk assessment and/or the methodology to be used to develop that data be referred to the Safe Drinking Water and Toxic Enforcement Act Scientific Advisory Panel (hereinafter the "Panel") for a pre-review. (C-5, p. 2.) Section 12705 (e) of these regulations already appears to accomplish this purpose by providing for a review during the development of data. Pursuant to that section, the members of the Panel must be provided copies of the initial statement of reasons for the adoption of a proposed no significant risk level. This document will likely include a description of the data to be used and the methodology applied to develop the data. The Agency intends that this information will be provided to the Panel members sufficiently in advance of the adoption of any no significant risk level that the Panel members will have ample opportunity to make comments. Therefore, a pre-review of data or methodologies to be used by the Agency in developing proposed no significant risk levels does not appear to be necessary and, in fact, would be duplicative.

Another commentator recommended an amendment to provide not only that the determination be based on evidence of comparable scientific validity to the evidence used for listing, but also that it be made in a manner designed to provide a realistic and plausible estimate of risk, neither seriously overestimating or underestimating risk. (Exh. 8, p. 8.) The adoption of this recommendation would create more confusion than clarity. The term "plausible" is defined as "seemingly or apparently valid, likely, or acceptable." (American Heritage Dictionary, Houghton

Mifflin Co., 2d College Ed., 1985, p. 950.) Of course, what seems valid, likely or acceptable is likely to vary significantly from person to person. The term "realistic" is defined as "tending to or expressing an awareness of things as they really are." (American Heritage Dictionary, Houghton Mifflin Co., 2d College Ed., 1985, p. 1030.) The difficulty with applying this concept to the assessment of risk from chemical exposures is that no one person knows how things really are. Much of the science employed is based upon theories which are constantly scrutinized and challenged. Therefore, this term would also provide little guidance. Moreover, since the true boundaries of risk are unknown, risk assessors often adopt a conservative approach in order to avoid underestimating the risk. This represents a "realistic" assessment of the extent of their knowledge. Accordingly, this recommendation was not adopted.

"Safe Harbor" Concept

Subsection (a) also provides that nothing in Article 7 is intended to preclude the use of evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in the article to establish that an exposure poses no significant risk. Therefore, the methodologies, data, principles, assumptions and levels described in the sections following section 12701 are not exclusive and do not prevent a plaintiff or defendant in an enforcement action from establishing "no significant risk" by other means. Since the methodologies, principles, assumptions and levels set forth in Article 7 are "deemed" to pose no significant risk when followed, in effect Article 7 provides a series of "safe harbors" upon which persons may base a claim of exemption from the requirements of the Act. This subsection provides that the "safe harbors" need not be utilized and persons may prove no significant risk by other means. However, such a showing must be based upon data, standards, methodologies, principles and assumptions which are scientifically valid as provided in the first sentence of subsection (a).

A similar approach was adopted by the Agency in its regulation regarding "clear and reasonable warnings." (22 C.C.R., § 12601.) That section provided minimum standards in order for warnings to be clear and reasonable, and provided "safe harbor" methods and messages which are deemed to be clear and reasonable, but also provided that the provision of the "safe harbor" methods and messages should not be construed to preclude a person from providing warnings in any other clear and reasonable fashion. Similarly, this article establishes a minimum requirement that the evidence and standards used are of comparable scientific validity to the evidence and standards supporting the listing of the chemical. "Safe harbor" levels and methodologies deemed to present no significant risk are provided. However, a person is permitted to use any data, standards, or risk assessment methodology, or apply any assumptions or principles desired to show that an exposure poses no significant risk. Where a "safe harbor" level or methodology is not used, it remains a question

of fact in any enforcement action whether the exposure poses no significant risk.

The July 29 proposal referred only to a person's use of evidence, standards or levels not described in Article 7 as a means of proving no significant risk. In its review of the comments to the July 29 proposal, it became clear that reference also needed to be made to risk assessment methodologies, principles and assumptions, since many commentators took this omission to signify that the risk assessment methodology, principles and assumptions expressed in section 12703 are mandatory. The Agency intends that section 12703 provide a "safe harbor" methodology, but does not necessarily represent the only method by which a person may determine a level of exposure which poses no significant risk. Accordingly, the March 29 proposal added specific reference to risk assessment methodologies, principles and assumptions.

Subsection (b) of section 12701 provides a menu of the "safe harbor" methods for determining no significant risk set forth in the regulations. The Agency has recognized in this article several alternative routes for arriving at a "no significant risk" level. They are not, however, afforded equal dignity. It is intended that some methods, such as the use of the no significant risk levels in section 12705 when available, will supersede many of the other methods identified, though not all. Subsection (b) is intended to afford persons enforcing the Act and persons in the course of doing business an easy reference to the use of the regulations which follow section 12701.

Generally, a determination of the "safe harbor" level posing "no significant risk" may be made (1) through the performance of a risk assessment as provided in section 12703, (2) by a determination that the exposure is to a specific chemical by a route, such as ingestion, which poses no significant risk of absorption of the chemical, or (3) the application of specific no significant risk levels set forth in the regulations or other California or federal law. Where specific "no significant risk" levels are to be applied, the regulation establishes a preference for those levels which are adopted pursuant to section 12705 and, in the absence of such levels, permits the use of levels adopted by other California and federal regulatory agencies for other regulatory purposes, levels developed for certain ubiquitous trace elements, and levels approved by the federal Food and Drug Administration for food, drugs, cosmetics and medical devices.

One commentator recommended that subsection (b)(3)A. should include an exception for foods, drugs, cosmetics and medical devices. (Exh. 4, p. 3.) Adopting this recommendation would, in effect, mean that levels adopted for purposes of the Act would not apply to these products. The Agency believes, however, that in most cases where federal or state law governing these products provides specific exposure levels, the federal or state level will be more stringent than the level adopted for purposes of the Act. Thus, where federal or state law provides specific levels,

the adoption of an exception appears to be unnecessary. Where federal or state law does not provide specific levels, then the Agency believes that the purposes of the Act would be better served by providing levels which can be applied to exposures to these products.

Risk Assessment v. Exposure Assessment

The July 29 proposal provided that the "determination that exposure to a listed chemical poses no significant risk under this article may be made: . . . ." The menu of methods followed. Upon further review, there appeared two problems with this language. First, the methods listed in the menu did not describe how it could be shown that a particular exposure poses no significant risk. Rather, the methods describe how to arrive at the level which, assuming lifetime exposure, would pose no significant risk. The application of that level to a particular exposure requires the application of section 12721, which is not listed in the menu. Second, the language suggested that the methods listed are mandatory, rather than optional "safe harbors." In order to clarify that the menu refers only to methods of arriving at levels or amounts of chemical which pose no significant risk, and that the methods offer "safe harbors," the first clause of subsection (b) was amended in the March 29 proposal to read:

> "A level of exposure to a listed chemical, assuming daily exposure at that level, shall be deemed to pose no significant risk provided that the level is determined: . . . ."

Several post-hearing commentators objected to a perceived conflict created by the reference to "assuming daily exposure at that level." In particular, these commentators contended that this phrase conflicts with the provision of section 12721(d)(4) requiring lifetime exposure for consumer products to be calculated using the average rate of intake or exposure, since many consumer products do not result in daily exposure. (P-3, p. 1; P-8, p. 2; P-10, p. 1; P-11, p. 4.)

In order to determine whether an exposure poses no significant risk, it is first necessary to determine the potency of the chemical on the basis of epidemiologic or animal bioassay data. Epidemiologic data assesses the impact of the chemical upon groups of individuals who have been exposed to it over identifiable periods of time. Animal data is generally derived from tests in which a relatively small group of animal subjects are exposed to the chemical for most or all of their lives. The resulting data is generally refined to arrive at a daily dose which likely will produce a predictable carcinogenic response in humans. Accordingly, the levels expressed in sections 12705, 12709, and 12711, or the results of an assessment pursuant to section 12713, are expressed in terms of daily exposure.

The next step in the process is to determine the extent of the exposure to the chemical caused by the person in the course of doing business. This is accomplished by determining the average rate of intake or exposure to that category of consumer products, and comparing it to the daily exposure level which poses no significant risk. If the average daily exposure does not exceed the no significant risk level, then the exposure meets the exemption test of the Act. Thus, there is no conflict between section 12701 as amended and section 12721. Each describes a different step in the process of determining whether an exposure poses no significant risk. No amendment appears to be necessary.

12701(b)(3)B.

In the July 29 proposal, subsection (b)(3) provided guidance on the use of levels set forth in the regulations. Subparagraph B of that subsection provided that if no specific level was set forth in section 12705, sections 12709, 12711 or 12713 could be applied. Upon further consideration, it became evident that the language of this subparagraph was not consistent with the scheme actually set forth in the regulations, since these sections by their own terms are limited in their application. In order to make section 12701 more consistent with these other sections, the March 29 proposal added to the end of subparagraph B. the phrase "unless otherwise provided."

One post-hearing commentator objected that the addition of "unless otherwise provided" to this paragraph would prevent persons whose business involves foods, drugs, cosmetics and medical devices from utilizing the levels set forth in section 12711(a)(2). (P-1, p. 2.) Others questioned the need for this amendment. (P-10, p. 2; P-11, p. 4.) In the July 29 proposal, section 12711 specifically provided that the levels therein constituted levels of no significant risk "[e]xcept as otherwise provided in section 12705, 12707, 12709 and 12713." Section 12711, therefore, was not intended to provide levels applicable in every case, but rather was intended for application to chemical exposures not covered by the other specified sections.

Section 12713, which applies to foods, drugs, cosmetics and medical devices, was adopted in part because the existing state and federal regulatory schemes provide standards which apply specifically to all such products. Since section 12713 refers to standards applicable to all such products, there is no reason to have the levels in in section 12711 also apply. Further, as a general rule, when there is a specific rule which conflicts with a more general one, the specific rule prevails. Section 12701 contains a general provision as to section 12711's applicability. Section 12711 is much more specific in this regard. Therefore, the provisions of section 12711 on the applicability of the section were intended to prevail over the provisions of section 12701. Also, section 12713 contains standards specifically applicable to foods, drugs, cosmetics and medical devices. For these products, the specific standards were intended to prevail

over the more general standards in section 12711. The phrase "unless otherwise provided" was added by the March 29 proposal to clarify that the specific was indeed intended to prevail over the general.

It is the intention of the Agency, in utilizing the existing regulatory scheme for foods, drugs, cosmetics and medical devices, that failure to comply with the existing standards will provide a basis for liability and enforcement proceedings under the Act, just as it would provide a basis for liability under the existing scheme. Accordingly, the phrase "unless otherwise provided" has been retained in the final regulation.

This same commentator recommended alternative language as follows:

> "(a) Except as otherwise provided in section 12705, and with respect to any food, drug, medical device, or cosmetic after the determination of no significant risk in section 12713 expires, levels of exposure deemed to pose no significant risk may be determined as follows:"

Such a revision does not appear to be necessary. As indicated above, section 12713 applies to <u>all</u> foods, drugs, cosmetics and medical devices. In the event of a repeal of that section, there would be nothing in section 12713 to supersede section 12711, and section 12711 would apply, unless one of the other specified sections were applicable.

Article 7 does not expressly address no significant risk levels, routes of exposure or conditions of use for every chemical which is subject to the Act. Subsection (c) makes clear that the absence of levels, routes of exposure or conditions of use in the regulations does not mean that there is no level for the chemical which poses no significant risk.

The concept of "no significant risk" under the Act may bear similarity to other statutory standards for which specific chemical exposure, discharge, tolerance or contamination levels may have been developed for the protection of the public health. Where levels are established in this article, persons regulated under or enforcing other statutory standards or levels may be motivated to contend that such other levels are superseded or undermined by the levels established herein. Subsection (d) is intended to clarify that the levels set forth in these regulations are established solely for the purposes of implementing the Act, and not to affect any other regulatory program.

One commentator recommended that subsection (d) be expanded to state that the regulations under Proposition 65 do not establish that an exposure has actually taken place in a specific circumstance or that a cancer or reproductive toxicant risk has actually been incurred by a specific individual. (C-23, p. 2.) Such an amendment, however, appears to be unnecessary. Whether

an exposure has taken place has little to do with this regulation, which addresses the exemption to the warning requirement imposed upon persons causing exposures. Further, the adoption of "safe harbor" no significant risk levels has no bearing on exposures to specific individuals except to the extent that a particular exposure exceeds the "safe harbor" levels. The apparent thrust of this recommendation is to sanction in the regulations the unlimited use of warnings, even where none is required by the Act because the exposure is insignificant. This would encourage the use of warnings where the risk is insignificant. The proliferation of meaningless warnings was a major fear of opponents of the Act during the campaign surrounding its adoption. (See Official Ballot Pamphlet, General Election, November, 1986, Rebuttal to Argument in Favor of Proposition 65.) Accordingly, this recommendation was not adopted.

Section 12703

This section provides a methodology for conducting quantitative risk assessments for the purpose of establishing a "safe harbor" no significant risk level. There are many reasons why it is important to have such a methodology in these regulations. For many chemicals, levels which pose no significant risk may not have been developed either for purposes of the Act or for other regulatory programs. Thus, persons in the course of doing business who use such the chemicals may not have specific "safe harbor" numbers on which to rely in determining compliance with the Act. As a result, such persons may unnecessarily alter their business practices, or provide unnecessary warnings which may dilute the effectiveness overall of warnings under the Act. Finally, some persons in the course of doing business may disagree with the specific "safe harbor" levels, or other levels, which have been established because, for example, such levels may have been derived from data which is outdated. These persons may choose to conduct their own risk assessments to ascertain a level posing no significant risk.

There are many variables in the performance of a risk assessment. There are competing theories about the mechanisms of carcinogenesis. There are often several studies or sets of data of varying quality upon which the assessment may be based. There are a variety of assumptions which may need to be applied. There are sometimes differences of opinion about what risks are significant. By selecting data of high quality, choosing more conservative and accepted theories and assumptions, and assigning significance to levels of risk in a manner tending toward the protection of the public health, persons in the course of doing business should be able to calculate "no significant risk" levels which can withstand scientific or legal challenge. However, persons enforcing the Act and persons in the course of doing business may be motivated to base their analyses upon less reliable data, less accepted or more controversial theories and assumptions, and assignments of "significance" to exposures at

excessively low or high levels to suit their immediate purposes and objectives.

The purpose of this section is to provide a collection of assumptions and principles for the conduct of risk assessments which will, if observed, produce a no significant risk level which is conservative, reliable, consistent with the purposes of the Act and which reliably pose no significant risk of cancer. The section is not designed to require that these assumptions and principles be applied to all assessments used when proving the absence of significant risk. Persons may conduct risk assessments in any manner they choose. However, in order for a risk assessment to provide a "safe harbor" level, it must be conducted in accordance with this section.

"Safe harbor" risk assessments need not be performed in a rigid fashion. Rather, it is intended that each default assumption or principle set forth in section 12703 apply only in the absence of a scientifically more appropriate principle or assumption.

Subsection (a) requires that risk assessments intended to establish a "safe harbor" no significant risk level be based upon evidence and standards of comparable scientific validity to the evidence and standards which formed the basis for the listing of the chemical. The listing of chemicals under Health and Safety Code section 25249.8(b) must be based upon "scientifically valid testing according to generally accepted principles." Therefore, the same standard applies to the performance of risk assessments used to support a showing of "no significant risk."

The subsection goes on to provide certain default assumptions or principles which must be observed in the absence of a scientifically more appropriate assumption or principle in order to arrive at a "safe harbor" level.

The default assumptions set forth in the regulation are based on methods currently used by the state Department of Health Services as set forth in "Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale," November 1985, by the state Department of Food and Agriculture as set forth in "Risk Assessment Guidelines: Oncogenicity," March 9, 1987, and by federal agencies (e.g., the Environmental Protection Agency's Carcinogen Assessment Group) in conducting risk assessments. These methods are generally accepted by the scientific community.

One commentator objected that the default assumptions are inappropriate and unnecessary, and could be interpreted as creating a presumption in favor of the assumptions. This commentator recommended that the phrase "and made in a manner designed to provide a plausible and realistic estimate of risk, neither seriously overestimating or under estimating risk" be added at end of first sentence. (Exh. 8, p. 8-9.) It was clear from this comment that the status of the risk assessment methodology described in section 12703 as a "safe harbor" only was not well delineated in the July 29 proposal. Accordingly,

the March 29 proposal amended section 12701(a) to specifically provide that no significant risk can be proved on the basis of risk assessment methodologies, principles and assumptions other than those described in section 12703. Such a risk assessment would not provide a "safe harbor," but is nevertheless available in the event of an enforcement action. Whether compliance with a level based upon such an assessment would in fact prove no significant risk would be a question for the court to decide.

This same commentator complained that it is not clear from section 12703(a) that the default assumptions are not intended to apply where they are not appropriate. The commentator therefore recommended two alternative solutions:

1) delete the second sentence of subsection (a), along with subparagraphs (1) through (8), and replace with: "If there are sufficient data to perform a quantitative risk assessment, all available information meeting these criteria, including but not limited to information on pharmacokinetics, interspecies, interdose, and interroute extrapolations, cancer potency, physiologic and metabolic considerations, shall be used to choose the most appropriate mathematical model. The degree of uncertainty in the above factors should be used to determine whether it is more appropriate to use the upper 95% confidence limit, or the maximum likelihood estimate to describe potency."

2) In the alternative, amend the second sentence to state: "In the absence of other scientifically appropriate principles or data that meet these criteria, the following default assumption may be considered if they meet these criteria and are appropriate for the particular chemical and data in question:" (Exh. 8, pp. 14-15.)

In order to clarify that the default assumptions and principles, or scientifically more appropriate assumptions and principles, are required only for "safe harbor" assessments, the March 29 proposal amended subsection (a) to provide, "A quantitative risk assessment which conforms to this section shall be deemed to determine the level of exposure to a listed chemical which, assuming daily exposure at that level, poses no significant risk." The Agency believes that, in conjunction with the March 29 amendment to subsection 12701(a), the regulation now clearly provides that the default assumptions need not be used in all assessment of no significant risk.

Another commentator recommended that the regulation clarify that alternative assumptions and methodologies can be incorporated into risk assessments whenever they are scientifically appropriate for the particular substance and data in question, and that there is no need to show that an alternative assumption is "more" appropriate than a default assumption. (Exh. 7, Appendix A, pp. 1-2.) While this suggestion might be appropriate if the purpose of section 12703 were to describe how any risk assessment to show no significant risk might be done, it is not appropriate for a regulation which produces a "safe harbor" level

deemed by the Agency to pose no significant risk of cancer assuming lifetime exposure at that level. The default assumptions and principles are well-established scientific concepts which the Agency can be assured will produce a reliable result consistent with the purposes of the Act. To allow any scientifically appropriate assumption or principle as an alternative to the default assumptions, rather than scientifically more appropriate alternatives, could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, this recommendation was not adopted.

This same commentator recommended that the default assumptions consistently be described as principles that "should" be considered, and recommended the substitution of the word "should" wherever the word "shall" is used, as in subparagraphs (a)(4), (a)(5), and (a)(6). (Exh. 7, p. 35.) However, use of the word "should" implies that assumptions and principles other than the default assumptions and principles may be used even where they are not more appropriate. Again, this could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, the March 29 proposal did the opposite of this recommendation. References to the word "should" were changed to "shall." Thus, whenever the "safe harbor" methodology is employed the default assumptions and principles, or scientifically more appropriate assumptions and principles, must be used.

Several post-leaving commentators objected to the deletion of the requirement that the default assumptions or principles "should be considered," and its replacement with "shall apply." (P-1, p. 6; P-9, p. 1; P-11, p. 6.) Again, section 12703 provides a "safe harbor" methodology which is designed to produce a result which the Agency can be assured will pose no significant risk within the meaning of the Act. In order to maintain this level of assurance, it is essential that the described methodology not only be considered, but in fact be applied. Flexibility is permitted where other assumptions or principles are scientifically more appropriate. Further, one of these commentators points out (P-1, p. 6.), there is no requirement that the "safe harbor" methodology be used to prove no significant risk. Accordingly, the amendment has been retained.

One commentator recommended that the regulation list the following as acceptable guidance documents for the conduct of risk assessments: (1) National Research Council, Risk Assessment in the Federal Government: Managing the Process", National Academy Press, 1983, (2) Office of Science and Technology Policy, Executive Office of the President, Chemical Carcinogens; A review of the Science and Its Associated Principles, March 14, 1985 (50 Fed. Reg. 10371), and (3) DHHS Committee to Coordinate Environmental and Related Programs (CCERP), Risk Assessment and Risk Management of Toxic Substance, A report to the Secretary, April 1985. This commentator further recommended that the regulation should outline a risk assessment process which fully

implements the recommendations and principles contained in the guidance documents to assure that a weight of the evidence approach is among the options available under the Act. (C-35, p. 5.) Of course, any approach of comparable scientific validity to the evidence and standards supporting the listing of the assessed chemical is an option available under the Act. (See section 12701(a)) Therefore, the adoption of specific references appears to be unnecessary.

One commentator recommended that risk assessments be validated by the Panel. (Exh. 4, p. 4.) The purpose of this section is to permit persons to conduct their own risk assessments which will produce a "safe harbor" no significant risk level. If the Panel were required to validate these assessments, it could easily consume all of the Panel's time and prevent the Panel from carrying out its functions already set forth in section 12305 (22 C.C.R., § 12305.). The Agency intends to adopt "safe harbor" no significant risk levels in section 12705 which will be based upon risk assessments conducted in accordance with the methodology set forth in section 12703. Section 12705 provides for a review by the Panel of any level proposed for adoption by the Agency. Therefore, it appears unnecessary to have the Panel conduct additional reviews. This recommendation was not adopted.

Two post-hearing commentators recommended that the reference to "principles or assumptions scientifically more appropriate" be changed to "equally or more appropriate." (P-1, p. 6; P-11, p. 6.) Arguably, this does not constitute a comment on a post-hearing change, since the requirement that alternative assumptions and principles be more scientifically appropriate was contained in the July 29 proposal. The commentator's failure to make its objection during the comment period to that proposal forecloses any objection at this stage of the regulatory process, and the Agency is not obligated to respond to the comment.

Nevertheless, the Agency again points out that the "safe harbor" methodology in this section is designed to provide a result which the Agency can with assurance conclude would pose no significant risk within the meaning of the Act. In order to maintain this level of assurance, the Agency believes that it is necessary to require that alternative assumptions or principles be scientifically more appropriate. The commentator complains that it may be difficult to prove that another principle or assumption is "more" appropriate than the default. The Agency can find nothing difficult with this burden. It simply entails proof that there is a scientific basis for concluding that the default assumption or principle may be less appropriate in a particular situation, and that an alternative assumption or principle is more appropriate. Accordingly, this recommendation was not adopted.

One post-hearing commentator expressed its concern that the first sentence of section 12703(a) could be read to mean that a level derived from a risk assessment under section 12703 is the only allowable no significant risk level, and that, for the same

reason, the policy level of one excess case of cancer in a population of 100,000 applies only to such risk assessments. (P-11, p. 3.) This was not the Agency's intention, and represents too confined an interpretation of the regulation. As section 12701(b) makes clear, a level of exposure to a listed chemical shall be deemed to pose no significant risk provided that it satisfies one of the enumerated sections. As section 12701(a) further makes clear, nothing in Article 7 shall preclude a person from using risk assessment methodologies or levels not described in Article 7 to establish that a level of exposure to a listed chemical poses no significant risk. Plainly, section 12703 was intended to provide a methodology to derive a "safe harbor" level only, not a binding number for all purposes.

Default Assumptions and Principles

Paragraph (a)(1) provides that animal bioassay data sets used for quantitative risk assessments must conform to generally accepted scientific principles, such as thoroughness of experimental protocol, the relevance of dosing to human exposure, etc. These examples are offered for purposes of illustration, and are not intended as a limitation. The intended purpose of this provision is to assure that the data upon which "safe harbor" risk assessments are based are of high quality.

In the July 29 proposal, it was provided that animal studies "should" meet generally accepted scientific principles. However, use of the word "should" implies that assumptions and principles other than the default assumptions and principles may be used even if they are not more appropriate. Again, this could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, as indicated above, the March 29 proposal changed the word "should" to "shall." Thus, whenever the "safe harbor" methodology is employed, the principle in subsection (a)(1), or scientifically more appropriate assumptions and principles, must be observed.

One commentator recommended that, if possible, results from risk assessments based on animal data should be compared to real world human data. (C-30, p. 2.) This is already provided for in the July 29 proposal. When an animal bioassay is selected as the basis for a risk assessment, the degree to which dosing resembles the expected manner of human exposure must be considered. (12703(a)(1).) Physiologic, pharmacokinetic, and metabolic considerations may be taken into account. (12703(a)(7).)

Paragraph (a)(2) makes provisions similar to paragraph (a)(1) applicable to epidemiologic data. Again, the factors of data selection specified in the paragraph are offered for purposes of illustration, and are not intended as a limitation.

One commentator recommended that conclusions drawn from epidemiological data should be based on statistical analyses that are sound, health endpoints that are measurable and well defined, and exposures that reflect real world conditions. (C-30, p. 9.)

To the extent that the soundness of statistical analysis and the measurability of health endpoints represent evidence and standards of comparable scientific validity to those which provided the basis for the listing of the assessed chemical, they appear to be proper considerations when selecting epidemiologic data as a basis for risk assessment. However, they need not be specifically mentioned in this section, since the factors of data selection set forth in the section are offered by way of illustration only, not as a limitation. The reference to "real world conditions" appears to be too vague, since it is unclear what conditions would be considered a reflection of the "real world."

Two commentators recommended that the regulations express a preference for human data where available. (C-35, p. 8; C-30, p. 9) The preference of the Agency is for data which provides the most appropriate basis for the conduct of the risk assessment. In some cases the data may be derived from humans in others from animals. A preference for human data, simply because it is available, may not provide the most appropriate basis. Therefore, this recommendation was not adopted.

In the July 29 proposal, it was provided that epidemiological studies "should" be appraised to determine whether they are appropriate. However, use of the word "should" implies that assumptions and principles other than the default assumptions and principles may be used even in the absence of more appropriate assumptions and principles. Again, this could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, as indicated above, the March 29 proposal changed the word "should" to "shall." Thus, whenever the "safe harbor" methodology is employed, the principle in subsection (a)(1), or scientifically more appropriate assumptions and principles, must be observed.

Paragraph (a)(3) provides that the "safe harbor" risk analysis should be based upon the most sensitive of the studies which, under paragraphs (a)(1) and (a)(2), are deemed to be of sufficient quality. Because of the wide range of sensitivity to chemicals observed in humans, it is likely that the response of the most sensitive study will be representative of the response of some individuals. In the absence of a scientifically more appropriate assumption, basing risk analysis on the most sensitive study will provide an appropriate level of protection to humans.

One commentator objected that the most sensitive study may not be indicative of the likely human response, and recommended that this paragraph be amended to read: "Risk analysis should be based on the most appropriate study deemed to be of sufficient quality." (C-36, p. 4) However, if it is scientifically more appropriate to base the assessment on a study other than the most sensitive one, this may be done and the "safe harbor" effect of the result preserved. Therefore, it does not appear necessary to adopt this recommendation.

Another commentator objected to the use of the most sensitive data even when biological and pharmacokinetic data indicate that a less sensitive species handles the compound in a way that is far more similar to humans than does the more sensitive species. (C-35, p. 13) Again, if under these facts another assumption would be scientifically more appropriate than the assumption in this paragraph, such other assumption may be applied.

Another commentator objected that this assumption is not likely to produce a realistic assessment of risk. (Exh. 8, p. 10.) However, the purpose of this assumption is to produce a realistic assessment of the risk to sensitive individuals. The Agency has concluded that this approach is more consistent with the purposes of the Act, and is consistent with the concept of a "safe harbor."

One commentator recommended that, as an alternative, the regulation derive an estimate that corresponds to the central tendency of the risk estimates from various data sets; a mean or median value, perhaps weighted according to the degree to which each individual estimate is thought to reflect the human risk. (Exh. 7, Appendix A, p. 7.) The Agency has concluded that, since this is a "safe harbor" default principle, a more conservative approach which protects sensitive individuals should be retained. A person may derive estimates in the manner described pursuant to section 12701(a), but no safe harbor is given.

In the July 29 proposal, it was provided that risk analysis "should" be based on the most sensitive study deemed to be of sufficient quality. However, use of the word "should" implies that assumptions and principles other than the default assumptions and principles may be used even in the absence of more appropriate assumptions and principles. Again, this could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, the March 29 proposal changed the word "should" to "shall." Thus, whenever the "safe harbor" methodology is employed, the principle in subsection (a)(1), or scientifically more appropriate assumptions and principles, must be observed.

Paragraph (a)(4) provides that the result obtained from the most sensitive study shall be applicable to all routes of exposure, except those routes for which the results are irrelevant. Absent studies demonstrating a relationship between different routes of administration and differences in carcinogenic response by those routes, it is appropriate to assume that a chemical that is carcinogenic by ingestion is also carcinogenic by other routes, such as inhalation, and vice versa.

Absorption studies may reveal that a chemical administered by a particular route will be poorly absorbed. If according to generally accepted principles data obtained from such an exposure route are irrelevant to exposures by other routes, this assumption may yield and a different data set may be more

appropriate. However, when scientific interpretations of these data allow predictions of exposure by other routes, the assumption should apply and the data ought to be utilized.

One commentator recommended that this paragraph say "should," rather than "shall." (Exh. 7, p. 35.) However, use of the word "should" implies that an assumption or principle other than the default set forth in this paragraph may be used even in the absence of a scientifically more appropriate assumption or principle. Again, this could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, the March 29 proposal did the opposite of this recommendation. The reference to the word "should" was changed to "shall." Thus, whenever the "safe harbor" methodology is employed, this default assumption or principle, or a scientifically more appropriate assumption or principle, must be used.

One commentator objected that, in the absence of data showing no differences, the more likely assumption is that there will be differences in potency across routes of exposure, making interroute extrapolations inappropriate. (Exh. 7, Appendix A, p. 8.) It is unclear what makes this the more "likely" assumption. Generally speaking, it is prudent risk assessment policy to assume that if a substance causes cancer when administered by ingestion, it will cause cancer when inhaled, and vice versa. (See "Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale," California Department of Health Services November 1985, p. B-21.) In adopting this "safe harbor" methodology the Agency intends that "prudent risk assessment policy" be observed. Where local administration of a chemical does not result in systemic exposure, it may be scientifically more appropriate to depart from this assumption, and the regulation permits such departure. However, it should be noted that, in the selection of data conducting the risk assessment, one consideration is the degree to which dosing resembles the expected manner of human exposure. Thus, if human exposure is anticipated to be oral, and the available data are from dermal administration which does not result in systemic exposure, the study may not provide an adequate basis for the risk assessment.

Another commentator recommended that the test route of exposure most closely resembling the expected route of human exposure should be determinative in assessing animal bioassay data otherwise of comparable quality for risk assessment purposes. (C-44, p. 8.) This concern appears to have been partially addressed in subparagraph (1), which includes as a consideration in the selection of data the degree to which dosing resembles the expected manner of human exposure. The approach of subparagraph (1) appears to be less rigid than this recommendation and, therefore, preferable.

Another commentator recommended that paragraph (4) be amended to read: "If the results obtained from the most appropriate study

deemed to be of sufficient quality indicate a significant risk, the results of the study shall be applicable to those exposure routes which were the subject of the study. (C-36, p. 5.) In effect, the adoption of this recommendation could result in a no significant risk level inapplicable to most routes of exposure. The Agency believes that greater flexibility is desirable.

Paragraph (a)(5) provides "safe harbor" assumptions for the extrapolation of animal bioassay data, which is normally based upon responses to high doses of the subject chemical, to low-dose responsiveness. The absence of a carcinogenic threshold is assumed, and the use of no-threshold models is prescribed. Due to the nature of the carcinogenic process, a dose level below which a carcinogenic response is not expected (a "threshold" level) cannot, generally speaking, be experimentally verified at this time. The initial target for carcinogenic action appears to be genetic material or other macromolecules, and there is evidence that carcinogenesis may commence in a single cell. Even assuming that a threshold level exists, it is likely that the threshold dose for the most sensitive individual will approach a zero dose. Therefore, in the absence of data to the contrary, it appears more appropriate to assume that no threshold exists, and that any dose presents some risk.

In the absence of extrapolation models which are appropriate for use according to generally accepted scientific principles, this paragraph requires the linearized multistage model, with the upper 95 percent confidence limit of the linear term deemed the most appropriate for expressing the upper bound of potency. This model is based on the theory that several distinct changes are necessary to transform a normal cell into a malignant one, and that human cancer can arise from such a single transformed cell. The linearized multistage model forces a linear term in the estimation of the upper confidence limits, and produces a conservative result. However, where data are available on the time of appearance of individual tumors, time-to-tumor models may provide more accurate estimates of carcinogenic effect. This is particularly the case when the toxicity of the test substance causes the premature death of the subject.

In the July 29 proposal, it was provided that the assumptions and principles in subsection (a)(5) "should" be utilized. However, use of the word "should" implies that assumptions and principles other than the default assumptions and principles may be used even in the absence of more appropriate assumptions and principles. Again, this could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, as indicated above the March 29 proposal changed the word "should" to "shall." Thus, whenever the "safe harbor" methodology is employed, the principle in subsection (a)(1), or scientifically more appropriate assumptions and principles, must be observed.

One commentator objected contending the assumptions of no threshold, linearized extrapolation and use of the 95 percent

upper confidence limit on potency estimate are not likely to produce a realistic assessment of risk. The commentator therefore recommended that this paragraph be revised to indicate that (1) the assumption of the absence of a threshold dose and the use of no-threshold models are not required if scientific evidence supports an alternative approach and (2) an upper-bound, linearized multistage model is only preferred where it is appropriate for the particular substance and data in question. (Exh. 8, pp. 10-15.)

Other commentators made similar objections and recommendations. (See, e.g., C-30, p. 10; C-37, p. 18.) One recommended that where data exist on the mechanism of carcinogenicity of the particular substance suggesting the existence of a threshold, use of those data would be scientifically appropriate in assessing a no significant risk level. (Exh. 7, Appendix A, p. 10.) Another recommended that the Agency add after "utilized": unless a threshold has been scientifically demonstrated and accepted by the scientific community (IARC, NTP, etc.), since the section appears to assume that no threshold for carcinogens will ever be demonstrated or accepted by the scientific community. (C-12, p. 1.)

As indicated above, the Agency adopted to section 12701 in its March 29 proposal to address concerns about the application of the default assumptions to all risk assessments. The default assumptions, or assumptions scientifically more appropriate, are required only where the development of a "safe harbor" no significant risk level is desired. Nothing prevents the development of risk assessments outside the "safe harbor" methodology, or their use in proving no significant risk. Further, the "safe harbor" default assumptions are not rigid, but may yield to scientifically more appropriate assumptions. Therefore, the proposed amendments appear to be unnecessary.

While some strongly support the linearized multi-stage model, which is used by the Department of Health Services, and the use of the upper 95 percent confidence limit (C-27, p. 2.), other commentators objected to the "safe harbor" requirement that a linearized multistage model for extrapolation from high to low doses, with the upper 95 percent confidence limit of the linear term expressing the upper bound of potency, be utilized. The objections were made on the ground that these assumptions are very conservative and generally overestimate risk. (Exh. 7, Appendix A, p. 10; C-35, p. 12; C-42, p. 1-2; C-30, p. 9.)

As one commentator put it, the linearized extrapolation model is too conservative and is inappropriate for extrapolating chemical carcinogenesis, since it was developed to the reflect the apparent dose-response relationship observed in radiation carcinogenesis. Chemical carcinogenesis is different because (1) chemical agents are inhibited by physical transport barriers, while radiation reaches cell nuclear material without such inhibitions, (2) many chemical agents require metabolic activation; radiation does not, (3) unlike radiation, the body

has various detoxification, excretion and repair processes that operate on chemical agents, and (4) chemical reactions are modulated by the limited molecular energies available from the reactants to overcome activation energy. Thus, linearized extrapolation may not be appropriate for chemical carcinogenesis (C-37, p. 20.)

The use of this linearized multi-stage model in the assessment of chemical carcinogenesis is well-established. (See "Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale," California Department of Health Services, November, 1985.) Further, as indicated above, the Agency adopted language in its March 29 proposal to address concerns about the application of the default assumptions to all risk assessments. The default assumptions, or assumptions scientifically more appropriate, are required only where the development of a "safe harbor" no significant risk level is desired. Nothing prevents the development of risk assessments outside the "safe harbor" methodology, or their use in proving no significant risk. Further, the "safe harbor" default assumptions are not rigid, but may yield to scientifically more appropriate assumptions. Therefore, the proposed amendment appears to be unnecessary.

Moreover, the Agency believes that the use of a no-threshold approach, in the absence of evidence that another approach is scientifically more appropriate, contributes to a result which is consistent with the purposes of the Act.

One commentator recommended that the regulation permit the results of both the upper 95 percent confidence limit on risk as well as the maximum likelihood estimate (best estimate) and the lower confidence limit to illustrate the range of possible risk estimates. (Exh. 7, Appendix A, p. 11.) However, this would provide little assistance in arriving at a specific level which could be deemed to pose no significant risk. The purpose of this regulation is to permit some certainty. Persons would be left with a range of possible risk estimates, and different persons would use differing extremes of the range depending upon the objectives. Accordingly, this recommendation was not adopted.

One post-hearing commentator objected that the March 29 proposal required that the default assumption or principle provided in this paragraph "shall" be applied, rather than "should be considered." (P-2, p. 1.) Again, section 12703 provides a "safe harbor" methodology which is designed to produce a result which the Agency can be assured will pose no significant risk within the meaning of the Act. In order to maintain this level of assurance, it is essential that the described assumptions and principles be applied. Flexibility is retained in the "safe harbor" methodology by providing that alternative assumptions or principles may be utilized where their application is scientifically more appropriate. Further, there is no requirement that the "safe harbor" methodology be used to prove no significant risk. Accordingly, the amendment has been retained.

Paragraph (a)(6) provides that the results of low dose extrapolation must be expressed in milligrams of chemical per kilogram of body weight per day. This is the typical measure of exposure in carcinogenicity studies, and the expression of assessment results in a uniform and familiar manner is an important element in arriving at a result which is consistent with the overall risk assessment scheme. Thus, where experimental exposures are expressed in other units (e.g., parts per million of chemical in air or diet), an appropriate conversion to milligrams per kilogram of body weight per day is required to provide a standard for conversion to human exposures.

This paragraph also provides a formula for interspecies scaling and, in the alternative, provides a default factor of 14 when extrapolating mouse data to humans, and a factor of 6.5 when extrapolating rat data to humans. Both the formula and the default factors are based on the State Department of Health Services' "Guidelines for Chemical Carcinogen Risk Assessments."

With the apparent understanding that this paragraph places restrictions on the conduct of all risk assessments made for purposes of the Act, several commentators objected to the prescribed method for interspecies extrapolation. (Exh. 7, Appendix A, p. 12; Exh. 8, p. 10.) Some recommended alternative approaches which would produce "more accurate" results. (C-35, p. 12.) Of course, if another approach is scientifically more appropriate than a surface area scaling factor, then it may be utilized to calculate a "safe harbor" no significant risk level. Nothing prevents persons from conducting risk assessments for purposes of the Act which rely upon alternative approaches so long as those approaches can be justified.

In the July 29 proposal, it was provided that the assumptions and principles in subsection (a)(6) "should" be utilized. However, use of the word "should" implies that assumptions and principles other than the default assumptions and principles may be used even if they are not more appropriate assumptions. Again, this could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, the March 29 proposal changed the word "should" to "shall." Thus, whenever the "safe harbor" methodology is employed, the principle in subsection (a)(1), or scientifically more appropriate assumptions and principles, must be observed.

One commentator recommended that the correct units of potency are <u>reciprocal</u> milligrams per kilogram per day. (C-44, p. 8.) This observation is correct. Accordingly, paragraph (6) was amended in the March 29 proposal to provide that potency shall be expressed in reciprocal milligrams of chemical per kilogram of bodyweight per day.

Paragraph (a)(7) allows the use of physiologic, pharmacokinetic and metabolic considerations in inter-species, inter-dose and inter-route extrapolations, where such data may be taken into

account with confidence. The susceptibility of different animal species to a given chemical may vary due to differences in metabolism and pharmacokinetics. This provision allows the use of such data to support the validity of extrapolations between species and routes of exposure. It may also be used to identify limitations of those extrapolations. For example, such data may support or contradict the relevance of results obtained by one route of exposure to other routes. However, the data must be of sufficient quality that it may be taken into account with confidence.

Paragraph (a)(8) provides specific assumptions about human body weight for purposes of the "safe harbor" no significant risk level. Once the dose or number of milligrams of chemical per kilogram of body weight necessary to produce a particular response has been determined, it is necessary to determine the daily dose level as expressed in milligrams per day. This is accomplished by multiplying the number of milligrams by the assumed body weight of the exposed population. Where the cancer risk from a chemical is to the public in general, the assumed human body weight is equivalent to the assumed body weight of the adult male (i.e., 70 kilograms). This is appropriate because cancer is generally regarded as a risk resulting from exposure over a 70-year lifetime. However, where the cancer risk applies to a certain subpopulation, such as women or infants, different assumptions must be made. The specific assumed body weights set forth in the regulation are derived from the Report of the Task Group on Reference Man, published in 1975 by the International Commission on Radiation Protection.

One commentator recommended that the reference to "Women with Conceptus" be amended to "Woman with Conceptus." (C-12, p. 1. This amendment was made in the March 29 proposal.

In the July 29 proposal, it was provided that the assumptions and principles in subsection (a)(8) "should" be utilized. However, use of the word "should" implies that assumptions and principles other than the default assumptions and principles may be used even in the absence of more appropriate assumptions and principles. Again, this could erode the certainty which the Agency requires in order to deem that a level would pose no significant risk. Accordingly, the March 29 proposal changed the word "should" to "shall." Thus, whenever the "safe harbor" methodology is employed, the principle in subsection (a)(1), or scientifically more appropriate assumptions and principles, must be observed.

Subsection (b) provides the level of human response at or below which the Agency concludes there is "no significant risk" from the exposure. It defines the "no significant risk" level as the level which results in no more than one excess case of cancer in an exposed population of 100,000 (1×10^{-5}), assuming lifetime exposure at the level in question. The 10^{-5} risk level is commonly used as an acceptable risk level by many regulatory agencies. Generally speaking, regulatory levels range from 10^{-4}

to 10^{-6} or lower. (See C. C. Travis, et al., "Cancer Risk Management: A Review of 132 Federal Regulatory Decisions," Environmental Science and Technology, Vol. 21, No. 5, p. 415 (1987).) These fluctuations are often imposed due to differences in the methodologies employed in the underlying risk assessment. Under these regulations, it is intended that risk assessments based upon default assumptions will produce fairly conservative results. In effect, applying a 10^{-5} standard to a conservative risk assessment can produce the same result as applying a 10^{-6} standard to an assessment employing less conservative methodologies.

Moreover, the application of a 10^{-5} standard for the purposes of the Act appears to be no less protective than the application of a 10^{-6} or lower standard under other regulatory programs. The purpose of the Act is to regulate exposures to specific chemicals. The purpose of most other programs is to control the risk from a particular medium, such as food, water or air. Therefore, these other programs must, in adopting a particular standard, consider issues of mixture, interaction, bioconcentration and transformation of several chemicals as part of the cumulative risk presented by chemicals in that medium. This often demands that the standards applied under such programs to the chemicals of concern be individually set at more restrictive levels.

Accordingly, the Agency believes that setting the level of "no significant risk" for "safe harbor" risk assessments at a 10^{-5} level will in effect provide no less protection than other levels set at 10^{-6} or lower, and is consistent overall with the regulation of cancer-causing chemicals.

Although some commentators supported this provision (C-35, p. 9; C-44, p. 2.), two commentators objected that the risk level permitted is too high, failing to take into account the cumulative effect of exposures from different sources, and urged that individual exposures regulated by the Act should be limited to a one-in-a-million risk. (C-27, p. 2; C-48, p. 2.) The Act prohibits exposures and exempts them where the exposure would pose no significant risk. Thus, the apparent focus of the Act is the exposure and the purpose of the Act to make each person in the course of doing business responsible for his or her exposure. To set the risk level on the basis of cumulative exposures would, in effect, make persons in the course of doing business partially responsible for the exposures caused by others. This does not appear to be authorized.

One commentator recommended that subsection (b) be amended to replace "one excess case of cancer in an exposed population of 100,000" with "an increased risk of cancer of one in 100,000." (Exh. 8, p. 16.) The Agency has concluded that its language provides a clearer statement of its purpose.

At the time of the July 29 proposal, the Agency had proposed a regulation which would provide that, to the extent that a listed

chemical is contained in water received from a source other than a public water system, no discharge or release within the meaning of the Act occurs when the water is discharged or released, provided that the water is returned to the same source of water supply, or has been treated to specified standards for the chemical. One purpose of this regulation was to address toxic chemical clean-ups. The Agency was informed that in most clean-ups, water is taken up, treated, and returned to the same source of ground or surface water. The proposed regulation would prevent liability for chemicals received in the water.

Subsequent to the July 29 proposal, the Agency came to recognize that some clean-ups would not be covered by that proposed regulation. It was not the intent of the voters adopting the Act that the discharge prohibition impede actions to clean polluted ground or surface waters. The arguments surrounding the adoption of the Act make repeated references to businesses which "put" or "dump" toxic chemicals into sources of drinking water, and claim that the Act would "[k]eep these chemicals out of our drinking water." The Act does not appear to have been intended to apply where a business removes these chemicals from drinking water.

It is the intention of the Agency that ground and surface water cleanups not be impeded. Accordingly, the March 29 proposal added to subsection (b) certain ordered or supervised clean-ups as an example of a situation in which sound considerations of public health support an alternative level to the level calculated to result in one excess case of cancer in a population of 100,000 (10^{-5})as the level which represents no significant risk.

One post-hearing commentator objected to this change. (P-11, p. 7.) First, the commentator claims it is inappropriate to raise the "cleanup issue" without providing an opportunity for comment. Second, the commentator contends that it involves an issue beyond the scope of the July 29 proposal. However, the addition of an illustrative example to a provision contained in the original proposal is certainly not beyond its scope, and to object because the illustration is related to the "cleanup issue" could prevent the use of any illustration, since each would be related to some issue.

Third, the commentator recommends that only alternative levels higher than 10^{-5}, such as 10^{-4}, should be referenced, since courts or governmental agencies may require a cleanup to discharge at a lower level than 10^{-5}, contending that this may interfere with cleanups. However, the Act is clear that any discharge or release must, to be exempt, be less than significant in amount <u>and</u> comply with all other laws and applicable regulations, permits and orders. Moreover, if a cleanup has been ordered at a lower level, it is difficult to see how the imposition of the same level under the Act will interfere with cleanup as ordered.

Finally, this commentator recommends that the levels selected in voluntary cleanup operations should receive the same treatment. The Agency believes that court or governmental oversight provides the necessary degree of assurance that, for purposes of the "safe harbor," the no significant risk level selected will be consistent with the purposes of the Act. However, it should be emphasized that nothing in these regulations is intended to prohibit voluntary cleanups.

Section 12705

Subsection (a) provides that exposure to a level of a listed chemical at or below the level set forth for the chemical in subsection (b) poses no significant risk within the meaning of the Act. The purpose of this section is to set forth specific "safe harbor" no significant risk levels established in accordance with Article 7.

The establishment of "safe harbor" no significant risk levels is necessary. Most businesses do not have the resources to conduct their own risk assessments, whether or not under the principles of section 12703. Yet each business with ten or more employees needs the ability to determine whether its activities comply with the Act, require a warning, or require change. If the Agency did not establish specific "no significant risk" levels, these businesses might have no way of making this determination.

One commentator objected that the "safe harbor" levels under section 12705 will override other methods of establishing "no significant risk" under Article 7, and recommended that they be just another alternative. (C-18, p. 10.) In fact, this observation is only partially true. The levels set forth in this section would not supersede a level developed using the "safe harbor" risk methodology. Nor would they supersede the determination that a chemical poses no significant risk by a particular route of exposure. To the extent that the levels in this section will supersede other levels, the levels in this section will be developed specifically for purposes of the Act and in accordance with this article. Other levels set forth in these regulations are often based upon other regulatory programs, which may have purposes differing from those of the Act. Thus, the Agency believes that the levels set forth in this section will provide a more appropriate basis for a "safe harbor" exemption from the requirements of the Act.

One commentator objected that no levels were adopted. (C-37, p. 17.) At this time, no such levels have been established. Until such levels are set, businesses may rely upon levels derived from other regulatory programs as provided in sections 12711 and following. The Agency has begun conducting risk assessments on a number of chemicals of particular concern to establish "no significant risk" levels calculated to result in no more than one excess case of cancer in an exposed population of 100,000. This section will be amended to include these levels after they have been determined. The Agency intends to conduct

these assessments according to the principles set forth in section 12703, which should result in levels which are both scientifically appropriate and consistent with the purposes of the Act.

One commentator objected that there is no basis upon which to conduct a quantitative risk assessment of beryllium, so no such assessment should be conducted. (C-30, p. 2.) Of course, if no level is established, then persons causing exposure or discharges must on their own prove that their actions or omissions pose no significant risk. By adopting these regulations the Agency is attempting to avoid that eventuality.

One commentator, in response to the suggestion by some that different standards be employed depending upon whether the level is to be applied to the discharge or the exposure prohibition, recommended that the same standards should apply for both discharges, releases and exposures. (Exh. 8, p. 16.) It is the intent of the Agency that the levels set forth in section 12705 apply to discharges, releases and exposures.

Subsection (c) requires the Agency to include the Panel in the rulemaking process establishing "no significant risk" levels in subsection (b) by providing them with notice and copies of proposed levels, along with copies of the supporting statements of reason. The Panel may submit comments to become part of the rulemaking file, and members of the Panel may comment individually. However, nothing requires that either the Panel or any of its members submit any comment on such a proposal.

This is consistent with a recommendation of the Panel and with the policy of the Agency to consult with the Panel on scientific matters. The Panel is composed of experts in a variety of disciplines related to the study of carcinogenicity and reproductive toxicity, and is an important resource which the Agency believes should be utilized. This section is intended to afford to the no significant risk levels proposed by the Agency a high quality scientific review.

One commentator recommended that no regulatory levels should be set under section 12705 until a public hearing is held before the Scientific Advisory Panel and a written recommendation is made to HWA by the Panel since the issues are scientifically complex and there is a compelling need to have consistent safety standards throughout the United States for nationally marketed products. (C-18, p. 10.) Another recommended that Panel approval of no significant risk levels should be required. (Exh. 8, p. 17.) This does not appear to be necessary. The authority to adopt regulations implementing the Act rests with the lead agency. Therefore, in order to adopt regulations, the lead agency must solicit public comment, which generally includes the conduct of a public hearing. To conduct separate hearings before the Panel would be duplicative. To require the Panel to provide the Agency with a written recommendation would place an unnecessary burden upon the Panel's time and resources. The July 29 proposal

provided the Panel the opportunity to comment upon any level proposed. This should provide ample opportunity for the Panel to address the scientific issues, and the Agency will need to respond to these comments. As for the need for consistent safety standards, consistency is just as likely to result from a process before the Agency as a process before the Panel.

Section 12707

Subsection (a) of this section provides that, where scientifically valid absorption studies conducted according to generally accepted standards or principles establish that absorption of a chemical through a specific route of exposure is low, so that exposure at or below applicable levels under current regulation by such route can be reasonably anticipated to present no significant risk of cancer, the Agency may designate the chemical as presenting no significant risk by such route. If so designated exposures, discharges and releases of the chemical resulting in exposure by that route which do not exceed applicable formal and informal regulatory levels are deemed to pose no significant risk within the meaning of the Act.

The "safe harbor" assumption for the assessment of carcinogenic risk, which finds expression in section 12703(a)(4), is to apply results obtained from one route of exposure to all routes of exposure. However, as expressed in section 12703(a)(7), when data are of sufficient quality that certain physiologic, pharmacokinetic, and metabolic considerations can be taken into account with confidence, those data may be used in the risk assessment for, among other things, interroute extrapolations. Section 12707 represents a specific application of the interaction between these principles.

Some commentators objected that the regulation does not reflect or provide for recognition that a chemical is "known to the State to cause cancer" only by a specified route. This, they contend, puts the burden on business to show no significant risk even though the chemical is not known to cause cancer by that route. (Exh. 8, p. 18; C-30, p. 15.) Similarly, other commentators recommended that the regulation include chemicals in accordance with remarks by the Panel regarding the route of exposure, specifically lead phosphate (injection only), methyl iodide (injection only), acetaldehyde (inhalation only), and methylene chloride (inhalation only). (Exh. 7, p. 37; C-18, p. 11; C-30, p. 2.) This regulation shifts no burden. The Act authorizes the listing of chemicals known to the state to cause cancer, not routes of administration. Once a chemical is listed, the Act places the burden on persons causing exposures or discharges of the chemical to demonstrate that the exposure or discharge poses no significant risk. (Health & Saf. Code, § 25249.10.)

As for the remarks of the Panel, the Agency has taken the position that these references were not intended to mean that the chemical poses no risk by other routes, but were intended to reflect the route of administration through which carcinogenicity

was determined and, at most, the absence of available data for carcinogenicity through other routes. (See letter to Wendell Kilgore, Ph.D., Chairman of the Panel, from Steven A. Book, Ph.D., dated 1/3/89.) In a letter dated February 9, 1989, Dr. Kilgore agreed with this position, stating: "When a panel member makes a recommendation he/she frequently states the route of exposure in the test animals. This certainly does not mean that the other unmentioned routes are safe; but most likely could mean that other routes have not been tested, or that the route of exposure in humans might be different and that this information, or the lack of it, should be taken into account in making a risk assessment." Accordingly, the Agency concludes that there is an adequate basis for excluding these other chemicals from section 12707, in the absence of data showing that absorption of a chemical through a specific route of exposure can be reasonably anticipated to present no significant risk of cancer.

One commentator objected to the limitation on the exemption levels consistent with current regulatory levels, some of which may have not been adopted through any formal regulatory process. (C-30, p. 15.) Regardless whether regulatory formalities have been observed, this section represents the extent to which the Agency can conclude with confidence that exposure by a particular route poses no significant risk. If some other regulatory agency has established a health-based exposure level for a chemical listed in section 12707, the presence of the level indicates a degree of systemic absorption. This regulation is predicated upon the absence of systemic absorption. Thus, where a level of exposure will result in absorption of one of these chemicals, the Agency cannot conclude that in fact the exposure poses no significant risk.

In the July 29 proposal, subsection (b) provided that three listed chemicals pose no significant risk by the route of ingestion: (1) beryllium and beryllium compounds, (2) cadmium and cadmium compounds, and (3) chromium (hexavalent compounds). The March 29 proposal included asbestos as another chemical which poses no significant risk by the route of ingestion. So long as the presence of asbestos, beryllium and its compounds, cadmium and its compounds, and compounds of hexavalent chromium are in compliance with all other administrative standards for those substances, the Agency views their presence in any situation by which they would be ingested to pose no significant cancer risk.

The reasons for this regulation are several-fold. First, the Agency believes the available data to suggest that the cancer risk from ingestion of these listed substances is minimal, principally due to the poor absorption of these substances across the intestinal mucosa and into the blood stream of those who may ingest them. Second, the Agency believes that, because many of these substances occur in nature, there is difficulty in identifying them, and there is difficulty in taking action to remove them, particularly when their presence may be widespread. Third, the Agency believes that current regulation of these

substances, where it exists, together with the evidence of poor absorption, should adequately protect the public any significant risk of cancer from such chemicals by the route of ingestion.

This regulation is based upon current scientific knowledge. Should the Agency acquire new information which establishes that the identification of a chemical in subsection (b) is inappropriate, it may remove the chemical from this section. Nothing in this section is intended to prevent the establishment of a no significant risk level under section 12705 for any chemical set forth in subsection (b) of this section. Further, this section presently applies only to exposure by route of ingestion. Those who would apply this section to discharges into sources of drinking water should pay attention to possible inhalation exposures which may result from the use of drinking water supplies for purposes other than drinking (e.g., showering).

One commentator objected that there is insufficient scientific basis for the conclusion that beryllium, cadmium, and their compounds, and hexavalent chromium, present no significant risk of cancer by the route of ingestion. (C-19, p. 3.) To the contrary, there appears to be considerable evidence.

Compounds of hexavalent chromium are included in subsection (b) because chromium is poorly absorbed from the gastrointestinal tract. The International Commission on Radiological Protection (Report of Committee II on Permissible Dose for Internal Radiation, Recommendations of the International Commission on Radiological Protection, ICRP Publication 2, Pergamon Press, New York, 1959), (ICRP Report) recommended use of an absorption value of 0.5 percent of the administered oral dosage from the gastrointestinal tract, as contrasted with a 25 percent absorption from the lungs. Further, the majority of the information on the carcinogenicity of hexavalent chromium compounds is based upon inhalation studies. Information derived from studies other than inhalation is limited. (California Department of Health Services, Report to the Air Resources Board on Hexavalent Chromium, December 9, 1985.)

Cadmium and its compounds are similarly limited in the absorption from the gastrointestinal tract. The ICRP Report recommended the use of 0.25 percent absorption across the gut, and 25 percent absorption across the lungs, a two order-of-magnitude difference. The information on the carcinogenicity of cadmium and cadmium compounds is also restricted to inhalation and injection studies.

Beryllium and its compounds were recommended for listing primarily because of the presence of positive data for carcinogenicity following the injection of those substances. The Agency believes it is appropriate to consider these substances as posing no significant risk via ingestion, for reasons similar to those cited for hexavalent chromium and cadmium; that is, gastrointestinal absorption is poor. The ICRP above recommended using 0.2 percent uptake from the gut and 25 percent from the

lungs. Deposition in bone from an oral exposure is given in the ICRP report as 0.064 percent, while deposition from an inhalation exposure is 8 percent. Positive data for carcinogenicity are lacking on ingestion studies.

One correspondent, during the time of informal comment period on interpretive guidelines issued by the Agency, viewed that beryllium ought to be treated as posing no significant risk by the route of inhalation. However, as evidenced above absorption and deposition in bone are significantly higher following inhalation than they are following ingestion. In fact, representatives of the beryllium industry indicated to the Agency that it is "well documented" that "beryllium, when introduced by inhalation, has produced tumors in animal species such as rats and monkeys." The Agency believes that these data cannot be ignored for purposes of its regulations. The federal Occupational Safety and Health Administration recently adopted in Part 1910 of title 29 of the Code of Federal Regulations occupational limits to address the carcinogenicity of airborne exposures to beryllium and its compounds, as well as a number of other substances. (54 Fed.Reg. 2332, 2679 (1/19/89.) If they choose, persons in the course of doing business may demonstrate the absence of significant cancer risk by inhalation by methods of quantitative risk assessment such as described in section 12703.

This same correspondent repeated this contention when commenting on this regulation and recommended that it be amended to provide that beryllium presents no significant risk of cancer by any route of exposure other than direct injection. (C-30, p. 13.) For the foregoing reasons, this recommendation was not adopted.

As for asbestos, the July 29 proposal had included in proposed section 12711 a "safe harbor" level for ingested asbestos of 140 million fibers per day. The March 29 proposal deleted this "safe harbor" level and included asbestos as a chemical which poses no significant risk of cancer through the route of ingestion so long as the levels are consistent with all standards, regulations, guidelines, action levels, licenses, permits, conditions, requirements and orders. The concern about the carcinogenicity of asbestos is most appropriately focused upon exposures through the route of inhalation. (*See comments of Panel at its meeting dated September 16, 1988.) The fact that the no significant risk level for ingested asbestos would be 140 million fibers per day, as proposed in the July 29 proposal, suggests that systemic absorption of the substance by the route of ingestion is low, and that the chemical poses no significant risk by that route.

One commentator recommended that the chemicals in the July 29 proposal should be deemed to pose no significant risk by the route of dermal exposure. (C-18, p. 10.) However, no absorption data was provided, and chemicals cannot be included in this section in the absence of appropriate absorption data. Accordingly, this recommendation was not adopted.

Section 12709

This section provides that, unless a specific "no significant risk" level has been established pursuant to section 12705, exposures to certain trace elements not exceeding specified amounts pose no significant risk.

There are some listed chemicals that are ubiquitous in nature. Because of their widespread existence, they are present in the air people breathe, the food they eat and the water they drink. These elements would be in the air, food and water, regardless of any past or present human activity, because of their occurrence in the environment.

The elements listed in section 12709 are ingested or inhaled in considerable quantities each day. For example, the International Commission on Radiological Protection's (ICRP) Task Group on Reference Man (ICRP Report No. 23, Pergamon Press, New York, 1975) identified the daily intake from air, food and water to be 1,000 micrograms of arsenic, 12 micrograms of beryllium and 150 micrograms of cadmium. More recently, the United States Environmental Protection Agency identified the daily intake of those elements to be 20 to 50 micrograms of inorganic arsenic per day. (US EPA, Health Assessment Document for Inorganic Arsenic, p. 2-23, 1984), 0.4 micrograms of beryllium per day (US EPA, Health Assessment Document for Beryllium, p. 3-16, 1986), and 50 micrograms of cadmium per day (US EPA, Health Assessment Document for Cadmium, p. 4-28, 1981).

Because these elements are ubiquitous, it is likely that virtually every exposure, whether through a product, the workplace or the environment, will contain some amount of the chemical. Persons in the course of doing business may be aware of their presence, but can do little or nothing about it. For example, persons in the course of doing business who produce paper products or fertilizers may find themselves with trace amounts of a number of substances in their products which were not necessarily added to those products as specific chemical ingredients, but are nonetheless there as a result of their presence in plants or soils.

If every person in the course of doing business warned about the presence of these chemicals, the public might be inundated with warnings which would provide little benefit and obscure other warnings about risks which are truly significant. Hence, the Agency believes it appropriate to treat ubiquitous trace elements differently than other listed substances. When a person in the course of doing business exposes an individual to a ubiquitous trace element which was contained in a raw material and was not specifically added as a chemical to the product, the Agency believes the "safe harbor" level ought to take into account the origin of that element, as well as the daily intake of the element. Therefore, the Agency has identified levels for several elements in subsection (b).

The levels in subsection (b) are derived from consideration of the average daily intake of the chemical. For arsenic, the level is 10 micrograms per day. This value is low compared to the daily intake of 20-1000 micrograms of arsenic from air, food and water. It is also 10 percent of the daily intake of arsenic allowed in drinking water, based on an intake of two liters of water per day and the maximum contaminant level of 50 parts per billion for total arsenic. For beryllium, the level is 0.1 micrograms per day. This value is low compared to the daily intake of 0.4-12 micrograms of beryllium per day. No drinking water standard exists for beryllium; hence, this comparison is not available. For cadmium, the level is one microgram per day. This value is low compared to the daily intake of 50-150 micrograms per day. Ingestion from drinking water at the maximum contaminant level would be 20 micrograms of total cadmium per day.

Again, the Agency emphasizes that these values are intended to be applied to the ubiquitous substances that are natural trace elements in raw materials and are not intended to be used for substances that are added as chemicals to products. Also, these values are intended to be used in the absence of levels posing no significant risk for the listed elements, or specific compounds of the listed elements, which will appear in section 12705.

One commentator recommended that the Agency suspend these levels until levels are set under section 12705. (C-8, p. 2.) The purpose of this regulation is to quantify those trace amounts of these elements which should not constitute a basis for concern by persons in the course of doing business. Suspending this "safe harbor" would leave persons with trace amounts of these elements in their products or exposures wondering whether they are in compliance with the law. Accordingly, these trace amount levels were retained.

Another commentator objected that the beryllium level is insupportable because it is not based upon studies which address the appropriate route of exposure (i.e., injection). (C-30, p. 19.) The beryllium level is based upon average daily intake and, since beryllium is listed as a chemical known to the state to cause cancer, intake may be calculated on the basis of all routes.

One commentator contended that the no significant risk level for beryllium via inhalation is five times the daily intake allowed for workers under either the federal or state occupational safety and health programs. (C-12, p. 2.) In fact, the allowable daily occupational intake is 16 micrograms, 160 times higher than the trace amounts level in this section. (8 C.C.R., 5155, Table AC-2.)

Section 12711

Section 12711 provides that, in the absence of specific levels in this article for chemicals in sources of exposure other than food, drugs, cosmetics and medical devices, no significant risk levels may be based upon levels developed by California or federal agencies for a carcinogen calculated to result in not more than one excess case of cancer in an exposed population of 100,000 persons, or upon levels for specific chemicals described in subsection (b) which correspond to a risk level of one excess case of cancer per 100,000 people exposed.

Subsection (a) permits the limited use of existing regulatory levels because persons in the course of business may already be complying with such levels. Provided that these levels afford a sufficient degree of human protection, these persons should be able to rely upon their compliance with existing law as an assurance that they are in compliance with the Act as well.

One commentator objected that the first sentence of this section is inconsistent with section 12701(b)(3)B and is technically incorrect. This commentator argues that a level established under proposed section 12711 can be overridden by a level established under section 12705, but is not overridden by proposed sections 12709 or 12713. This commentator recommends that section 12711(a) should be revised by deleting the reference to sections 12707, 12709, and 12713. (Exh. 7, p. 38-39.)

It was and continues to be the intention of the Agency that the levels in section 12709 and 12713 override the levels set forth in section 12711. Section 12711 very carefully states that for the products set forth in section 12713, section 12711 has no application. As for the perceived inconsistency with section 12701(b)(3)B, that section has been amended by including the words, "unless otherwise provided." Accordingly, if no level is provided in section 12705, a level set forth in section 12709, 12711 or 12713 may be used, unless otherwise provided.

One commentator recommended that the percentage cut-offs of 1 percent for hazardous substances and 0.1 percent for carcinogenic substances as set forth in the federal Hazard Communication Standard, are appropriate to establish "no significant risk" for mixtures under the Act. (C-37, p. 22.) While this may provide some guidance for occupational exposures in the absence of a more specific level at which the chemical presents a cancer hazard, it does not appear to be appropriate for other kinds of exposures.

One commentator recommended that the first sentence should not be designated as "(a)" and present paragraphs (1) and (2) should be redesignated as paragraphs (a) and (b). (Exh. 7, p. 38.) The Agency believes that the regulation is clearer in its present form.

One commentator recommended that levels posing no significant

risk for purposes of the Act be established on a health related basis only and not with reference to other regulatory levels which may not have been based upon health. (C-23, p. 2) Since subsection (a)(1) specifically refers to regulatory levels calculated to result in not more than one excess case of cancer in an exposed population of 100,000, it appears clear that the levels referred to are based upon health. If a person chooses to rely upon environmental standards which are more strict than health based numbers, the greater will be the likelihood that enforcement actions will not result.

One commentator recommended that the Agency make clear that the methodology and underlying data used in a quantitative risk assessment in support of a regulation, may be used to determine no significant risk for purposes of the Act, even if the actual regulatory level set by the federal or state agency's regulation was based on a risk greater than one in one hundred thousand. (C-39, p. 5.) Where the other laws do not provide adequate protection because the regulatory level is greater than a 10^{-5} risk, section 12701 still permits the use of the underlying risk assessment, and if the risk assessment conforms to section 12703, it could provide a "safe harbor" no significant risk level provided that level is calculated at a 10^{-5} risk.

Section 12711(a)(2) identifies some specific levels based on state or federal risk assessments. The levels listed here are based upon risk assessments performed by the California Department of Health Services for the California Air Resources Board, under the latter's Toxic Air Contaminant Program, or upon risk assessments performed by the United States Environmental Protection Agency's Carcinogen Assessment Group, unless otherwise indicated.

The specific levels include levels set forth below derived from state risk assessments, using assumed parameters of 20 cubic meters of air inhaled per day, and a 70-kilogram body weight for the exposed individual.

Asbestos (inhaled)	100 fibers per day
Carbon tetrachloride	5 micrograms per day
Chromium, hexavalent	0.001 microgram per day
Dioxin (TCDD)	0.000005 microgram per day
Ethylene dibromide	3 micrograms per day
Ethylene dichloride	9 micrograms per day
Ethylene oxide	2 micrograms per day

In the July 29 proposal, specific reference was made in the initial statement of reasons to the fiber size of asbestos. Specifically, it refers to fibers equal to or greater than 5 micrometers in length and 0.3 micrometers in width, with a length/width ratio of greater than or equal to 3:1. These fibers can be measured by phase contrast microscopy (PCM) and for historical reasons represent the basis for all recent asbestos risk assessments. Such fiber counts can be converted to total fibers measurable by transmission electronic microscopy (TEM) by

multiplying by 100 to 1,000. Hence, 5 fibers per cubic meter of air, as measured by PCM would equal 500 to 5,000 fibers per cubic meter of air, as measured by TEM, and 100 fibers per day, measured by PCM, would be the equivalent of 10,000 to 100,000 .pa fibers per day, measured by TEM. The March 29 proposal included this information in the regulation.

The March 29 proposal also deleted the reference to ingested asbestos, and amended section 12707 to address asbestos exposure by the route of ingestion.

The risk assessments relied upon for the levels described above are found in the following source documents:

California Department of Health Services, Report to the Resources Board on Asbestos, January, 1986.

California Department of Health Services, Report to the Resources Board on Hexavalent Chromium, December 1985.

California Department of Health Services, Report to the Scientific Review Panel (Air Resources Board) on Chlorinated Dioxins and Dibenzofurans, February 1986.

California Department of Health Services, Report on Ethylene Dibromide to the Scientific Review Panel (Air Resources Board), April 1985.

California Department of Health Services, Report on Ethylene Dichloride to the Scientific Panel (Air Resources Board), June 1985.

California Department of Health Services, Report to the Air Resources Board on Ethylene Oxide, September 1987.

The specific levels in section 12711 also include levels set forth below derived from federal risk assessments. The risk assessments performed by the federal government are found in the US EPA report, Health Assessment Document for Beryllium, 1987, Table 7-18, pp. 7-82 through 7-85. EPA routinely publishes a table of information containing the results of its carcinogenic risk assessments in its health assessment documents. The document relied upon is entitled "Relative Carcinogenic Potencies Among 59 Chemicals Evaluated by the Carcinogen Assessment Group as Suspect Human Carcinogens." Levels equivalent to one excess case of cancer per 100,000 people exposed for a 70-year lifetime were calculated from the cancer potencies published by EPA.

The level for formaldehyde gas is based upon an assessment conducted by the EPA's Office of Pesticides and Toxic Substances entitled Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde, April, 1987. The level for 2(di-ethylhexyl)phthalate (DEHP) is consistent with assessments of the EPA found in two documents, Drinking Water Criteria Document for Phthalic Acid Esters (PAEs)

Draft Document dated August, 1986 with Corrections as Received March 7, 1988, ECAO/OHEA, US EPA., Cincinnati, Ohio, and Health and Environmental Effects Profile for Phthalic Acid Alkyl, Aryl and Alkyl/Aryl Esters, Draft Document dated September, 1987, ECAO/OHEA, US EPA., Cincinnati, Ohio.

The specific levels derived from federal risk assessments are as follows:

Chemical	Micrograms per day intake
Acetaldehyde	90
Acrylonitrile	3.
Aldrin	0.04
Benzene	20
Benzidine	0.003
Benzo(a)pyrene	0.06
Beryllium Oxide	0.1
Beryllium sulfate	0.0002
Bis(2-chloroethyl)ether	0.6
1,3-Butadiene	0.4
Chlordane	0.5
Chloroform	9.
Coke oven emissions	0.3
DDT	2.
3-3'-Dichlorobenzidine	0.4
Dichloromethane (Methylene Chloride)	50
Dieldrin	0.04
Di(2-ethylhexyl)phthalate	80
2,4-Dinitrotoluene	2
Epichlohydrin	70.
Formaldehyde (gas)	15
Heptachlor	0.2
Heptachlor epoxide	0.08
Hexachlorobenzene	0.4
Hexachlorocyclohexane (technical grade)	0.4
Nickel refinery dust	0.8
Nickel subsulfide	0.4
N-Nitrosodi-n-butylamine	0.1
N-Nitrosodiethylamine	0.02
N-Nitrosodimethylamine	0.03
N-nitroso-diphenylamine	140
N-Nitrosopyrrolidine	0.3
N-Nitroso-N-ethylurea	0.02
N-Nitro-N-methylurea	0.002
Polychlorinated biphenyls	0.09
Tetrachloroethylene	14
Toxaphene	0.6
Trichlorethylene	60
2,4,6-Trichlorophenol	40.
Vinyl chloride	0.3

One commentator recommended that this section should provide that warnings are not required unless the limits of detection are exceeded, since the level for asbestos exposures is substantially below the level of reliable detection for measurement of asbestos fibers according to standard PCM and TEM measurement techniques. (C-1, p. 2; C-17, p. 3.) Similarly, another commentator recommended clarification that where the levels are not detectable, there cannot be significant amounts discharged or knowing and intentional exposure under the Act. (C-43, p. 2.)

Subsequent to the July 29 hearing, the Agency adopted an amended version of section 12901 of Title 22 of the California Code of Regulations. Section 12901 governs the methods of detection to be used under the Act. The amendments, among other things, added subsection (g), which provides:

> "(g) For purposes of Health and Safety Code Sections 25249.5 and 25249.6, no discharge, release or exposure occurs unless a listed chemical is detectable as provided in this section."

Under this provision, warnings would not be required unless the the chemical is present in the exposure, discharge or release in detectable amounts. Therefore, no further amendment in this section appears to be necessary or appropriate.

One commentator urged that, in the absence of specific references and data sources used for any promulgated no significant risk level, reliance on alternative levels (properly determined using accepted risk assessment methods) should constitute compliance. (C-37, p. 34.) As indicated in section 12701, nothing about section 12711 or any other provision of Article 7 is intended to preclude persons from establishing no significant risk by other means. This could include reliance on alternative levels determined using accepted risk assessment methods. However, this approach could not provide the basis for a "safe harbor." Exemption from the Act on this basis would be a question of fact.

One commentator recommended that the Agency suspend these levels until levels are set under section 12705. (C-8, p. 2.) Since it is not anticipated that levels will be adopted under section 12705 for several months, the deletion of the levels set forth in this section would mean that some persons in the course of doing business might have no basis for measuring their compliance with the Act. The levels in section 12711 were adopted to avoid undue hardship on the regulated community precisely because there are no levels yet in section 12705. Accordingly, this recommendation was not adopted.

Another commentator recommended that the Agency should provide specific levels for all listed chemicals at the time of listing. (C-45, p. 2.) Under the Act, once the state's qualified determine that a chemical has been shown to cause cancer, the chemical is "known to the state to cause cancer." (Health & Saf. Code, § 25249.8(b).) The Governor is obligated to revise the

list of chemicals known to the state to cause cancer or reproductive toxicity at least once each year. This necessarily means that little time may exist between the date of the determination that a chemical is known to the State to cause cancer and the listing of the chemical. Even where there are available risk assessments for the chemical, it may be impossible to have a specific no significant risk level by the time of the listing. This section embodies the Agency's attempt to provide chemical levels at least by the date that the prohibitions of the Act begin to apply to exposures to that chemical.

One commentator objected that the risk assessments are apparently based on upper confidence level calculations, and recommends the use of best estimates. (C-1, p. 5.) Ninety-five percent confidence limits have been traditionally used in regulatory toxicology as estimates that would not underestimate anticipated exposures. Since the Act, like other regulatory toxicology laws, is intended to protect the public, the Agency believes that this traditional approach is appropriate when providing a "safe harbor" no significant risk level.

Two commentators objected that a quantitative no significant risk threshold (which relies upon a "continuous exposure model") is impractical, and recommended that a procedural approach (such as implementation of an operations and maintenance (O & M) program) would be far more practical and more likely to enhance safety. (C-17, p. 3; C-25, p. 3.) While the Agency encourages the use of O & M programs as a means of keeping levels of chemicals below the level posing a significant risk, it appears to be more practical to set a target level, as in this regulation, and leave any determination whether a particular O & M program successfully keeps exposures below the target level to the courts. Further, it may be possible to devise O & M programs in only a handful of situations covered by the Act. Accordingly, this recommendation was not adopted.

Two commentators objected that the asbestos level is too low by a factor of at least 2.5. (C-17, p. 2; C-25, p. 4.) Another recommended that the Agency re-evaluate the asbestos level, since it is below the level accepted by OSHA, and is possibly below the level of accurate measurement. (C-45, p. 3.) As indicated above, subsequent to the July 29 hearing, the Agency adopted an amended version of section 12901 of title 22 of the California Code of Regulations, which governs the methods of detection to be used under the Act. The amendments, among other things, added subsection (g) to provide that no discharge, release or exposure occurs unless a listed chemical is detectable. Under this provision, warnings would not be required unless the the chemical is present in the exposure, discharge or release in detectable amounts. Therefore, if the asbestos level falls below the level of detectability, there is no exposure under the Act. Further, the asbestos level is based upon a careful analysis of risk conducted by the Department of Health Services. These commentators do not appear to challenge the validity of that assessment. Accordingly, there appears to be no reason to modify

the asbestos level.

One commentator recommended that the Agency clarify that either phase contrast microscopy (PCM) or transmission electron microscopy (TEM) air monitoring methods may be used to ascertain whether asbestos exposures are "significant" for purposes of the Act's warning requirements, and that only fibers longer than five microns in length should be counted when either PCM or TEM is used. (C-1, p. 1.) The Agency agreed with this comment. The July 29 proposal contained no reference to asbestos fiber size in the regulation. However, the initial statement of reasons did contain a footnote reflecting the fiber sizes which provided the basis for the level adopted. Due to the need to make this information more readily available, the March 29 proposal, as indicated above, set forth the information on fiber size in the regulation adjacent to the level for asbestos.

Several commentators objected to the levels adopted for arsenic, asbestos, benzene, beryllium, cadmium, carbon tetrachloride, chloroform, DDT, hexachlorobenzene, hexachlorocyclohexane (technical grade), hexavalent chromium, polychlorinated biphenyls (PCBs), and tetrachlorodibenzo-(p)-dioxin (TCDD). (C-42, p. 7; C-37, p. 24 (benzene); C-29 (hexavalent chromium); C-47, p. 2 (hexavalent chromium).) Again, the levels set forth in the regulation are not binding. If these commentators feel that the scientific evidence justifies a higher level, nothing prevents them from using that evidence to establish no significant risk. The levels set forth in this section are the result of carefully performed government agency assessments of risk and, in the view of the Agency, provide a sound basis for adopting a "safe harbor."

One commentator objected that the value for vinyl chloride is not consistent with that calculated by EPA - Cancer Assessment Group (EPA, 1984) nor by the State of California (California Department of Health Services, 1986). This commentator contended that the EPA Cancer Assessment Group calculated a risk coefficient (q_1*) of 0.0175 for vinyl chloride. Using this q_1* value the risk is 40 micrograms per day. This commentator further contended that DHS listed the potency of vinyl chloride as 0.004 $(mg/kg/day)^{-1}$ using mouse data, 0.1 using rat data and .02 for humans. Using these values the 10^{-5} risk is 175, 70, and 35 micrograms per day, respectively. The commentator also pointed to FDA's calculations based upon male and female rats (28 and 2.2 micrograms/day, respectively.) (C-9, pp. 1-2.)

The Health Assessment Document for Beryllium (November, 1987) contains Table 718, Relative Carcinogenic Potencies Among 59 Chemicals Evaluated by the Carcinogen Assessment Group as Suspect Human Carcinogens (pp. 7-82 to 7-85). This table provides a level for vinyl chloride of 2.3 $mg./kg/day^{-1}$. From this slope is calculated the level set forth in section 12711. If this commentator chooses to rely upon the older data or higher levels, it may do so, but it remains a question of fact for the court whether a significant risk is posed.

One post-hearing commentator objected that the March 29 proposal did not respond to any of its objections or recommendations submitted at the July 29 hearing, and that no statement of reasons accompanied the March 29 proposal. This commentator further contends that the March 29 proposal contains substantive amendments, in particular the addition of several "no significant risk" levels, which did not receive adequate notice. (P-4, p. 2.) Government Code section 11346.8(c) provides that no agency may amend a regulation "unless the change is sufficiently related to the original text that the public was adequately placed on notice that the change could result from the originally proposed regulatory action." The commentator apparently objects to the addition by the March 29 proposal of several new "safe harbor" no significant risk levels to section 12711, including beryllium oxide and beryllium sulfate.

The July 29 proposal of section 12711 included levels for 31 substances. The March 29 proposal added another 16 substances. As indicated in the initial statement of reasons, the original 31 "safe harbor" levels were based upon a number of Air Resources Board documents and the US EPA report, Health Assessment Document for Beryllium, 1987, Table 7-18, pp. 7-82 through 7-85. EPA routinely publishes a table of information containing the results of its carcinogenic risk assessments in its health assessment documents. The document relied upon is entitled "Relative Carcinogenic Potencies Among 59 Chemicals Evaluated by the Carcinogen Assessment Group as Suspect Human Carcinogens." With the exceptions of di(2-ethylhexyl)phthalate and formaldehyde gas, the values added to this section in the March 29 proposal were based upon the same EPA documents. Therefore, it cannot be said that this change is unrelated to the original text.

Further, the notice for the July 29 proposal described section 12711 in the informative digest as follows:

> "f. Section 12711. Levels Based on State or Federal Standards.
>
> "Here, it is established that no significant risk may be demonstrated by application of risk levels adopted by other state or federal agencies, if such levels are calculated to result in no more than one excess case of cancer in an exposed population of 100,000. Chemical-specific levels of no significant risk based on state or federal risk assessments are set forth."

This excerpt clearly states that the section contains levels based upon federal or state risk assessments. Accordingly, the public was adequately advised that the change could result from the original regulatory action.

Further, the Agency is under no obligation to adopt every recommendation made by commentators on a regulatory proposal. Pursuant to Government Code section 11346.7(b)(3), the Agency is

obligated to provide:

> "A summary of each objection or recommendation made regarding the specific adoption, amendment, or repeal proposed, together with an explanation of how the proposed action has been changed to accommodate each objection or recommendation, or the reasons for making no change."

This final statement of reasons satisfies this requirement Further, Government Code section 11346.8(c) provides:

> "If a sufficiently related change is made, the full text of the resulting adoption, amendment, or repeal, with the change clearly indicated, shall be made available to the public for at least 15 days before the agency adopts, amends, or repeals the resulting regulation."

There is no requirement that an additional statement of reasons be made available along with the changes. Accordingly, the demand of this commentator that the Agency withdraw the regulations and provide a statement of reasons with any future changes need not be obeyed. Since the notice provided by the Agency was consistent with the requirements of the Administrative Procedure Act, the commentators demand that the Agency comply with this law is unnecessary since the law has been satisfied.

Another post-hearing commentator objected that the 15-day notice provided was insufficient. (P-7, p. 1.) However, as indicated above, 15 days is the minimum required by law, and the approach of the anniversary of the publication of the notice for the July 29 proposal and hearing requires that the Agency proceed expeditiously to avoid the need for another hearing on this entire article.

The March 29 proposal proposed other amendments to incorporate the emergency amendments made to section 12711 by emergency rulemaking on October 11, 1989. Subsection (a)(3) was added as a specific example of state or federal levels at which the safety of drinking water is regulated. The amendment provides that drinking water maximum contaminant levels, drinking water action levels, and levels permitted by a Regional Water Quality Control Board in a water quality control plan or waste discharge requirement to be discharged shall be deemed to pose no significant risk within the meaning of the Act.

One commentator objected to the adoption of drinking water action levels and levels of the regional water quality control boards as levels posing no significant risk on the ground that they have never been formally adopted. (P-11, p. 9) An action level is the level at which an administrative agency will act under its general authority to carry out its statutory responsibilities. The Agency is unaware of any requirement that these levels be adopted by regulation. Further, it must be emphasized that the levels set forth in section 12711 are intended to provide a "safe

harbor" only, not a binding number. Persons may use any level they choose to establish that an exposure poses no significant risk. This section is intended to provide a refuge for those who do not have the resources to develop or establish their own level. The Agency has concluded that this is preferable to providing no level at all, particularly since the Act is self-executing.

This commentator also expressed concern that the drinking water levels might be utilized for purposes other than the Act. However, to do so would be inconsistent with subsection (d) of section 12701, which provides:

> "(d) This article establishes exposure levels posing no significant risk solely for purposes of Health and Safety Code section 25249.10(c). Nothing in this article shall be construed to establish exposure or risk levels for other regulatory purposes."

Section 12713

This section provides generally that, unless a specific no significant risk level is set forth in section 12705, a chemical in a food, drug, cosmetic or medical device poses no significant risk if the exposure through the food, drug, cosmetic or medical device is in compliance with all applicable federal and California safety standards.

The concept underlying this regulation was extensively considered over several months prior to its adoption as an emergency regulation. The Agency received and reviewed six petitions requesting the promulgation of regulations governing the applicability of the Act to food, drug, medical device and cosmetic products. Each of these petitions requested the Agency to promulgate regulations determining that compliance with existing statutory and administrative standards under state and federal food, drug, medical device and cosmetic safety laws is sufficient to determine that no warning is required under sections 25249.6 and 25249.10(c). Hearings on these petitions were conducted by the Agency, pursuant to public notice, in Sacramento and in Los Angeles on June 15, June 16, and July 17, 1987.

Subsequently, the United States Commissioner of Food and Drugs wrote the Governor on August 28, 1987, requesting that the Governor take into consideration the regulatory scheme Congress enacted in the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and urging the Governor to consider recognizing that the products regulated by the Food and Drug Administration (the FDA) under the FD&C Act "present no significant risk." Because of the importance of and the widespread interest in this matter, the Agency wrote the Chairman of the Scientific Advisory Panel on November 20, 1987, requesting the Panel's opinion on whether existing state and federal standards for food, drugs, medical devices and cosmetics constitute assurance that chemicals in

these products pose no significant risk within the meaning of section 25249.10(c). In accordance with this request, the Panel considered this matter on December 11, 1987 at its scheduled public meeting. The current Commissioner on Food and Drugs, a former Commissioner of Food and Drugs, a former director of the Food and Drug Administration's Bureau of Foods, a representative of the United States Department of Agriculture (the USDA), the Chief of the Food and Drug Branch of the state Department of Health Services, and a large number of interested individuals and organizations presented testimony. The Panel concluded that current state and federal regulation provides considerable protection for food, drug, medical device and cosmetic products and thus recommended that the existing state and federal statutory and administrative standards for these products be adopted as a determination of "no significant risk" pending the establishment of specific levels under the Act.

This regulation is based upon the recommendation of the Panel. The Agency finds that existing state and federal food, drug, cosmetic and medical device safety standards, if complied with, are sufficient to protect consumers from substances in such products that pose any significant risk of cancer within the meaning of section 25249.10(c), pending the establishment of specific "no significant risk" levels. The Agency's conclusion is based on the broad applicability of state and federal safety standards, as reflected in numerous regulatory decisions prohibiting or restricting the presence of carcinogens in such products.

In deciding to follow the recommendation of the Panel, the Agency has considered the fact that the safety of food, drugs, medical devices and cosmetics has been the subject of state and federal regulation, under statutory and administrative safety standards, for as much as 80 years. Applying the policy of preservation of existing statutory and administrative standards (Health & Saf. Code, § 25249.13), the general principles of comity among coordinate administrative agencies, the express legislative policy of uniformity in regulation of food, drug, medical devices and cosmetics in Health and Safety Code section 26204, and the policy favoring a construction of the Act which furthers the intent to make meaningful warnings about chemical hazards available to the public, the Agency has determined that existing safety standards under these state and federal laws should be utilized in establishing levels of "no significant risk" for carcinogens pending the establishment of specific levels for the chemical constituents and contaminants of foremost concern in such products.

Several commentators supported this approach. (Exh. 1, pp. 2-3; Exh. 3, p. 2.); C-4, p. 1; C-5, p. 3; C-7, pp. 1-3; C-8, p. 2; C-33, p. 3.) Three commentators objected to this approach and recommended its deletion. (C-19, p. 3; C-24, p. 1; C-27, p. 2.) Implicit in some of the supporting comments and most of the objections is the belief that, under this regulation, the mere fact that a product is regulated under certain federal or state

laws means that the product poses no significant risk. This is incorrect. This section refers to standards only. Each of these product categories is subject to some kind of administrative standard. In every case there are non-specific qualitative standards. In many cases there are specific quantitative standards. In order for a product to be deemed to pose no significant risk, it must be in compliance with all applicable administrative standards.

The fact that an administrative agency, such as the federal Food and Drug Administration (FDA), has not taken action against persons causing exposure to a product which may not be in compliance with the applicable administrative standards does not mean that the product poses no significant risk. The absence of administrative action may simply mean that the FDA has yet to discover the violation, or that the FDA has, for administrative reasons, decided not to take action. It cannot be taken as conclusive proof that the applicable standards have been met.

It is the intention of the Agency that an action under the Act be available to make certain that these standards are satisfied. Accordingly, the "safe harbor" afforded by this section is available only where all applicable administrative standards have been complied with. Public prosecutors or persons in the public interest may bring actions where such products result in exposures to listed chemicals. The defendant in such an action may prove compliance with all applicable administrative standards and avoid liability. If the defendant cannot show such compliance, then the "safe harbor" is not available, but the defendant may still attempt to prove that there is no significant risk within the meaning of the Act by some other means not reflected in the regulations.

One commentator recommended that the regulation be amended so as to apply to reproductive toxicity in addition to carcinogenicity. (C-44, p. 2.) The exemption provided under the Act for reproductive toxicants specifically provides that the exposure would have no observable effect "assuming exposure at one-thousand times the level in question." This assumption has often been referred to as a "safety" or "uncertainty" factor. Uncertainty factors are commonly used in reproductive toxicology to reflect the risk assessor's confidence in the data upon which a risk assessment is based. Since the quality of data varies from chemical to chemical, the uncertainty factor also varies, usually ranging from ten to ten thousand. However, under the Act the uncertainty factor is assumed to be one thousand. The Agency finds no counterpart to this mandatory uncertainty factor in existing federal or state safety laws governing foods, drugs, cosmetics or medical devices. There appears to be no basis for providing that compliance with existing state or federal standards signifies compliance with the Act. Accordingly, this recommendation was not adopted.

Subsection (a) plainly reflects that the authority to determine that a chemical exposure poses no significant risk under this

section is temporary. The regulation recognizes certain existing state and federal standards, but provides that the Agency may determine that those existing state and federal standards do not meet the requirements of sections 25249.6 and 25249.10(c) and may, by rulemaking, establish different standards for that purpose. The establishment of specific levels under section 12705 will preclude any determination regarding food, drugs, cosmetics and medical devices on the basis of existing levels or standards as specified in section 12713.

One commentator observed that the designation for paragraph (a) had been inadvertently omitted. (C-16, p. 2.) This omission was corrected in the March 29 proposal.

Two commentators recommended the deletion of the reference to "food safety laws." (Exh. 4, p. 3; Exh. 7, p. 43.) One further recommended that the reference be replaced with "safety laws applicable to the product in question." (C-16, p. 3.) In the March 29 proposal, the Agency did delete the reference to food safety laws and replaced it with "administrative standards applicable to the product in question." The term "administrative standards" was already defined in subsection (b)(5), and the definition makes reference to safety laws.

Several commentators objected that this section provides only an interim standard. (Exh. 1, p. 11-12; Exh. 4, p. 2; Exh. 7, p. 43; C-3, p. 2; C-18, p. 9; C-38, p. 7; C-44, p. 2; C-46, p. 2.) One commentator went so far as to conclude that findings in statement of emergency compel adoption of the regulation, and prevent its "phasing out." (Exh. 1, p. 11-12; Exh. 4, p. 2.) This section makes reference to administrative standards, which may include both specific and non-specific standards. The Agency has concluded that persons attempting to enforce and comply with the Act will enjoy greater certainty regarding compliance where the standards adopted are specific, rather than non-specific. Thus, the Agency is conducting risk assessments for the purpose of adopting permanent specific standards for specific chemicals of concern in food, drug, cosmetic and medical device products. The Agency has also encouraged persons to determine whether their products comply with available specific standards, and to develop their own specific standards for the chemicals which may be found in their products. It does not appear that this process would be furthered by the permanent adoption of non-specific standards. Accordingly, the regulation continues to provide that the standards provided by this section are interim.

One commentator objected that no timetable was provided in the regulation for the repeal of the interim standard. (C-47, p. 2.) Since the adoption of this standard, the Agency has published a timetable for the conduct of risk assessments for the purpose of adopting permanent standards for specific chemicals of concern in food, drug, cosmetic and medical device products. Once adopted, these permanent standards would supersede any standard referred to by this section. The Agency has also advised repeatedly that it intends to repeal the non-specific standards referred to in

this section one year following the scheduled completion of the risk assessments. The Agency intends to follow this schedule, but does not believe that it is necessary to adopt it as a part of the regulation.

Subsection (b) defines the four categories of products to which this section applies: food, cosmetics, drugs and medical devices. In each case, the definition is based upon applicable federal safety law. This makes section 12713 consistent with the federal law to which it refers and confines the scope of the regulation to identifiable categories for which standards exist.

Under existing federal and state law and precedent, the term "food" is defined broadly to encompass all substances that, in any way, find their way into the products that are consumed as food. Thus, it includes not only raw agricultural commodities (including meat, poultry and eggs) that are commonly regarded as food, and their natural chemical constituents, but also all of the chemical constituents and ingredients, of natural or synthetic origin, that result from the production or processing of those commodities.

Subsection (b) also broadly defines the term "administrative standards" to include all legal requirements that relate to the safety of these products imposed by the state or federal agencies responsible for administering those requirements. This avoids the need for repeated references in each subparagraph to statutes, regulations, action levels and other formal and informal legal requirements.

Food, drug, medical device and cosmetic products are subject to existing state and federal legal standards that come from two primary sources. First, these products are subject to statutory standards set forth in the laws themselves. These statutory standards apply to all four categories of products, including all constituents and ingredients of those products. There are no products that fall within these four categories that are not subject to these statutory standards. The legal requirements imposed by these statutory standards, moreover, are self-executing, and must be complied with even if there are no implementing regulations or other legal requirements. The definition of "administrative standard" includes these statutory standards. Thus, these statutory standards represent the first level of assurance that food, drug, medical device and cosmetic products pose no significant risk of cancer.

In addition to the state and federal statutory standards, there are thousands of other formal and informal legal requirements that are imposed by administrative standards adopted by the state and federal agencies responsible for administering the statutes involved.

One commentator objected to the definition of medical devices on the ground that warnings are not warranted for medical devices. (Exh. 4, p. 1.) Of course, the purpose of this regulation is not

to require warnings on such products. The purpose is to provide a "safe harbor" from the warning requirement for such products which are in compliance with all applicable administrative standards.

Subsection (c) provides that exposure to a chemical which is subject to specific administrative standards applicable to identified categories of chemicals shall be deemed to pose no significant risk within the meaning of the Act. Eight categories of chemicals subject to administrative standards under the FD&C Act are identified. These categories, which often include standards based on quantitative risk assessments for specific chemicals, contain restrictions on chemical risks which are comparable to those in the Act. For each category, all applicable administrative standards must be met before a chemical exposure will be considered to pose no significant risk.

Subparagraph (1) makes subsection (c) applicable to "food additives" within the meaning of the FD&C Act approved for use at a specified level. The FD&C Act requires that food additives intended for use as ingredients in food be approved as safe prior to such use. Premarket approval is also required for food additives that, through use in articles that contact food, such as packaging, become components of food. (21 U.S.C. §§ 321(s) and 348(a)(2).) Although the FD&C Act excludes certain substances from the category of food additives, those food substances are subject to other regulatory controls.

The term "food additive" encompasses thousands of food substances, including substances that are intentionally incorporated into food to achieve a specific function ("direct" food additives), substances that are used to process food but which have no specific function in the food itself ("secondary direct" food additives) and substances that migrate into food but that have no functional use in the food ("indirect" or "incidental" food additives). (21 C.F.R. § 170.3(e).) Only those added substances that are "accidental and unforeseeable" are regarded as falling outside the regulatory definition of "food additive." (39 Fed.Reg. 42743, 42744 (December 6, 1974).)

Food additives include food packaging materials that may migrate into and therefore become components of food. It is assumed that all packaging materials in contact with food may migrate into food and they are, therefore, presumptively classified as food additives. Such substances are excluded from the definition only upon a showing that the level of migration is sufficiently low that no more than a de minimis level of risk is presented to the public. (Monsanto Co. v. Kennedy, 613 F.2d 947 (D.C. Cir. 1979); 49 Fed.Reg. 36635 (September 19, 1984) (acrylonitrile in plastic bottles).) FDA regulations governing use of packaging materials in food contact applications are set forth at 21 Code of Federal Regulations, parts 170-199.

Any substance that is a food additive must be subject to a food additive regulation promulgated by FDA before it may lawfully be

used in food. The proponent of a food additive has the burden of showing that it will be safe under the conditions of its intended use. (21 U.S.C. § 348(a).) The FD&C Act contains a provision, the Delaney Clause, which reinforces this requirement by prohibiting the approval of a food additive that has been shown to induce cancer in man or animals. (21 U.S.C. § 348(c)(3)(A).)

Under FDA's "constituents policy," that agency will approve a food additive containing a constituent that is carcinogenic in animals only if it presents an "insignificant risk" of human cancer. (47 Fed.Reg. 14464 (April 2, 1982).) This policy was upheld in Scott v. FDA, 728 F.2d 322 (6th Cir. 1984). FDA considers a food additive containing such a constituent to be unsafe and thus illegal if it represents a "significant risk" of human cancer.

Subparagraph (2) makes subsection (c) applicable to substances in food generally recognized as safe. Normally, carcinogens will not be generally recognized as safe. Therefore, if a food is generally recognized as safe, it should be considered to pose no significant risk within the meaning of the Act pending the establishment of specific "safe harbor" no significant risk levels.

Subparagraph (3) makes subsection (c) applicable to substances in food sanctioned for use by the FDA or the USDA prior to 1958, since prior sanctions are generally based upon a determination of the safety of the use. Again, the exposure must comply with all applicable administrative standards. Thus, a failure to comply with the conditions of the prior sanction, a determination that the sanctioned substance in fact may render it injurious to health, or that a nonadded substance is ordinarily injurious to health would make this subparagraph and subsection (c) inapplicable.

One commentator recommended that the Agency add after "(21 U.S.C. § 71, et seq.)": "or the California Meat and Poultry Inspection Act (Food and Agricultural Code Section 18650 et seq.)" in order to include meat and poultry products which are not regulated under the federal acts. (C-13, p. 1.) Another commentator objected that the regulation fails to cite the Egg Products Inspection Act (21 U.S.C. §§ 1301 et seq.) among the statutes which regulate food substances and recommended that the preemptive effect of this Act be included in this paragraph. (C-31, p. 2.)

This section refers only to substances sanctioned for use in food prior to 1958. The references to the the FD&C Act, the Meat Inspection Act and the Poultry Products Inspection Act are derived directly from the FD&C Act. The July 29 proposal contained no reference to the California Food and Agricultural Code. Upon further review, the Agency determined that reference to this code would be appropriate, since the Sherman Food and Drug Law includes the California Food and Agricultural Code as a source of prior sanctions. (Health & Saf. Code, § 26013(d).)

Accordingly, the March 29 proposal amended subparagraph (3) of subsection (c) to include the California Food and Agricultural Code as a source of prior sanctions.

However, there does not appear to be any authority for referring to the federal Egg Products Inspection Act (EPIA) in this subsection dealing with prior sanctions. The regulation already exhausts the specified sources of prior sanctions. The FD&C Act refers only to the meat and poultry products inspection acts. The Sherman Food and Drug Law refers to these same acts, and the California Food and Agricultural Code. No reference is made to the Egg Products Inspection Act. As for the alleged preemptive effect of the EPIA, the Agency does not intend to address this issue in these regulations. Accordingly, the recommendation regarding the EPIA was not adopted.

Subparagraph (4) makes subsection (c) applicable to "color additives" within the meaning of the FD&C Act approved for use at a specified level. Exposure to such color additives must comply with all applicable administrative standards. The administrative standards which apply to substances used to color food, drugs, medical devices and cosmetics closely resemble those for food additives. The color additive standards require premarket safety testing and FDA promulgation of a color additive regulation approving any substance used to color food.

Before a color additive may be approved, there must be reasonable certainty that the additive does not pose a significant risk to human health. (21 U.S.C. § 376(B)(4).) The Delaney Clause precludes approval of any color additive shown to induce cancer in man or animals. (21 U.S.C. § 376(b)(5)(B).) Food that contains an unapproved color additive or an additive whose use deviates from the terms of any approval is adulterated under the FD&C Act. (21 U.S.C. § 342(c).)

Under Health and Safety Code sections 26203 and 26207, the FDA color additive regulations are automatically adopted and are independently enforceable as California law. The state also reserves the right to promulgate its own color additive regulations that differ from the FDA regulations.

Subparagraph (5) makes subsection (c) applicable to substances which are required in the production of food or which cannot be avoided by good manufacturing practices for which a specific tolerance level has been established. The exposure must comply with all applicable administrative standards.

Subparagraph (6) makes subsection (c) applicable to pesticide chemicals used in the production, storage or transportation of agricultural commodities for which a specific tolerance level has been established. The exposure must comply with all applicable administrative standards. Under FD&C Act section 408, a food is adulterated if it contains a pesticide residue that has not been approved as safe for use on that food. (21 U.S.C. § 346a.)

FD&C Act section 408 permits a tolerance for a pesticide only upon a determination that the permitted residue will not endanger human health. A tolerance or action level may also be issued under FD&C Act section 406 to permit a safe level of a pesticide residue in food other than the specific commodities on which its use has been approved under FD&C Act section 408, where the pesticide has drifted to other crops during application or has otherwise left a residue in the food. (21 U.S.C. § 346.) Tolerance levels for pesticides are established by EPA and EPA has issued guidelines for carcinogenic risk assessment. (51 Fed.Reg. 33992 (September 24, 1986).)

Federal pesticide tolerance regulations are automatically incorporated as state law under Health and Safety Code sections 26203 and 26205. The state also reserves the right to promulgate pesticide tolerance regulations that differ from those imposed at the federal level. Further, Health and Safety Code section 26205 was amended in 1984 to require the Department of Health Services to evaluate whether a pesticide tolerance, or exemption from tolerance, is sufficiently protective of the public health whenever certain events occur that raise concern about the safety of the pesticide.

Subparagraph (7) makes subsection (c) applicable to animal drugs within the meaning of the FD&C Act approved for use at a specified level. The exposure must comply with all applicable administrative standards. Federal and state administrative standards for animal drug residues limit levels of chemical exposure to eliminate significant risk. Substances administered to food-producing animals as feed or drugs, and which leave a residue in the human food produced by the animal, are subject to premarket approval under the FD&C Act. The procedures for approval of animal feed additives and animal drugs are similar to those applicable to ingredients of human food. (21 U.S.C. §§ 321(s), 348 and 360b.)

The primary inquiry under the standards is whether the residue of the substance in human food is safe. The statutory criteria include a Delaney Clause prohibiting the use of cancer causing additives. If an additive is found to induce cancer in animals, it may be approved only if no residue will be found, by methods of examination prescribed by FDA, in any edible portion of such animals after slaughter or in any human food yielded by or derived from the living animals. (21 U.S.C. §§ 348(c)(3)(A) and 360b(d)(1)(H).)

Health and Safety Code sections 26010, 26012, 26013 and 26021 regulate animal feed in the same manner as human food and animal drugs in the same manner as human drugs, and contain essentially identical authority over any residues in human food as exists under the FD&C Act.

Subparagraph (8) makes subsection (c) applicable to drugs. The exposure must be in compliance with all applicable administrative standards. Prescription drugs are subject to premarket approval

by the FDA or the Department of Health Services. Most are "new drugs" within the meaning of the FD&C Act and the Sherman Law, which cannot lawfully be sold unless they are subject to an approved new drug application (NDA). (21 U.S.C. §§ 321(p) and 355; Health & Saf. Code §§ 26021 and 26670.) The requirements for approval of an NDA are essentially the same under the state and federal laws, and drugs for which NDAs have been approved under the FD&C Act are deemed to comply with Health and Safety Code section 26670(a). These requirements apply not only to genuinely new drugs but also to generic copies of established medicines. (21 U.S.C. § 355(j).)

Three other categories of prescription drugs, which are also within the scope of the regulations, are subject to separate requirements for premarket approval imposed by federal law. These include insulin and antibiotics, which are subject to premarket approval whether or not they are "new drugs" under FD&C Act sections 506 and 507 (21 U.S.C. §§ 356 and 357.) and biological products (e.g., vaccines and blood products), which are subject to licensing requirements under the Biologics Act (42 U.S.C. § 262.). A very small number of prescription drugs first marketed before 1962 are still permitted to be sold without premarket approval of an NDA from FDA, but the FDA is proceeding to subject those products to the NDA requirements and has in the meantime imposed restrictions on changes in the formulation of those products. (21 C.F.R. §§ 201.200 and 310.6.)

FDA imposes elaborate requirements for determining the safety of new drug ingredients throughout the drug development process, from synthesis of a new chemical entity until final FDA approval of an NDA. These have been described in "The Food and Drug Administration's Process for Approving New Drugs," Report Prepared by the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology, 96th Cong., 2d Sess. (1980) (the "House Subcommittee Report").

The new drug approval process is divided into three major stages: preclinical research, clinical investigation and NDA approval. As summarized by the Commissioner of Food and Drugs in his testimony before the House Committee:

> "[T]he system that has evolved for approving new drugs ... is extremely careful and rigorous. Sponsors of new drugs, for example, must present FDA with toxicological data collected from animals before testing can be conducted in humans. Then carefully staged human tests are conducted under FDA guidelines that is intended to show that a drug is both safe and effective. Only when such thorough testing is completed and reviewed by FDA scientists is a new drug permitted to be marketed.

> "The more potent or potentially hazardous drugs . . . are used through the advice and oversight of a physician or other health care professional, and the labeling for the physician carefully describes the potential hazards of those products."

Substantial research must be undertaken on the chemical, pharmacologic and toxicologic properties of a new chemical entity in order to meet FDA prerequisites for beginning clinical research (i.e., testing of the drug in human volunteers). As the House Subcommittee Report states:

> "[The FDA requirements] affect the type and direction of research and other development activities which must be done once a new chemical entity is identified." House Subcommittee Report pp. 13-14.

The FDA investigational new drug ("IND") regulations require that such preclinical research include sufficient chemical information about the drug to set exact specifications, using sophisticated analytical techniques, to assure little or no variation in the entity. (21 C.F.R. § 312.23(a)(7.)

The IND regulations also require that, before clinical investigation may begin, sufficient pharmacology and toxicology information must be obtained through animal testing to justify use of the chemical in humans. (21 C.F.R. § 312.23(a)(8).) FDA has established both formal and informal guidelines that can include extensive animal testing before an IND can be submitted.

Once adequate preclinical research is completed, an IND can be filed to justify clinical investigation of the new chemical entity in humans, in preparation for filing an NDA. The NDA provisions impose regulatory requirements on the clinical investigations conducted pursuant to an IND. FDA regulations and guidelines establish requirements for evidence of safety and effectiveness for a new drug. (21 C.F.R. part 314.)

After the requirements for preclinical research and clinical investigation are complete, approval of the drug for marketing must be obtained. An NDA or other application for premarket approval must contain a complete list of all substances used in the manufacture of the drug product, including not only the active ingredient, but also inactive ingredients, trace contaminants, and intermediates and other chemicals used in the production process, whether or not they are present in the finished product. (21 C.F.R. § 314.50(d)(1).) Applicants must submit analyses demonstrating the identity and purity of products at key stages of the manufacturing process. Information on drug ingredients and manufacturing processes is scrutinized to determine whether potentially harmful substances or chemical by-products may be present in the finished drug product.

The requirements of the NDA approval procedure are supplemented by official compendia (the United States Pharmacopoeia and the National Formulary) which establish standards for the purity of ingredients used in drugs, and by FDA regulations that set forth detailed requirements for current good manufacturing practices ("GMP") in the manufacturing, processing, packing and holding of drugs. (21 U.S.C. §§ 351(b), 352(e), 352(g); 21 C.F.R. parts 210 and 211.) The GMP regulations govern all aspects of the production process, including personnel, facilities, equipment, control of components, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, returned and salvaged products and records.

The Agency recognizes that some drugs which may present a cancer hazard are allowed to be marketed with a mandatory warning if the beneficial properties of the drug outweigh the cancer risk. The Agency acknowledges that such drugs may pose a "significant risk" within the meaning of the Act and the use of such drugs should be preceded by a warning. Therefore, subsection (e) specifically provides that section 12713 shall not apply to any drug the labeling of which contains a statement that the drug causes or may cause cancer, whether in humans or animals. It would appear to make little sense to provide that a drug is exempted from warning on the ground of that it poses no significant risk when federal law requires its labeling to contain a cancer-related warning because it does in fact pose a significant risk.

As with prescription drugs, there are also systems of regulation that govern nonprescription drugs under state and federal administrative standards. A regulatory program has been established under the FD&C Act that ensure that nonprescription or over-the-counter ("OTC") drugs do not expose consumers to toxic substances. The program includes a recent review of the safety of all nonprescription drugs by expert panels, as well as procedures for prompt action to ban drugs from the market whenever new scientific evidence indicates that certain drugs or ingredients pose a medical risk to the consumer. As the Commissioner of Food and Drugs testified:

> "For over-the-counter drugs, we have been conducting an OTC Review for several years of OTC drugs, many of which have been widely used for decades. Under the guidance of expert advisory groups from outside government, we have carefully developed monographs that summarize our conclusions about the safety and effectiveness of those drugs. Those that are found by that process to be unsafe or ineffective are removed from the market."

This review is conducted by one of seventeen panels formed to review all OTC drugs within therapeutic classes of OTC drugs, which under the prescribed procedures address the issue of carcinogenicity. FDA requires consideration of the following:

> "... which tests are adequate to prove the safety of a particular drug.... If it is decided that carcinogenicity and reproductive studies are necessary for a particular drug, then that fact will be reflected in the panel recommendations [to FDA]." (37 Fed.Reg. 9464, 9469 (May 11, 1972).)

Although active ingredients were the main focus of the panels' inquiry, the panels also considered the safety of inactive ingredients where appropriate. Information considered by the panels included safety data on finished drug products, consisting of active ingredients, inactive ingredients and trace constituents. FDA regulations require that an OTC drug contain "only suitable inactive ingredients which are safe in the amounts administered." (21 C.F.R. § 330.1(e).)

After analyzing the scientific data and testimony, the panels submitted reports on 58 OTC drug categories to FDA. These reports evaluated the safety and effectiveness of the reviewed drugs according to the "best scientific evidence available." (37 Fed.Reg. 9464, 9469 (May 11, 1987); 21 C.F.R. § 330.10 (a)(4).) Based on these reports FDA is establishing monographs for categories of OTC drugs. When a final monograph becomes effective, an OTC drug must conform to all of the conditions established by the monograph for its drug category or it will be subject to regulatory action (unless the monograph is amended or the manufacturer obtains an approved NDA). (21 C.F.R. § 330.10(b).) These conditions should assure that OTC drug products which comply with federal administrative standards pose no significant risk of cancer.

OTC drugs which are not "new drugs" within the meaning of the FD&C Act (and, thus, subject to the NDA process previously above) must meet statutory requirements of general recognition of safety and effectiveness. (21 U.S.C. § 321(p).) FDA has taken the position that the requirements for proof of general recognition of safety and effectiveness are the same as those for proof of the safety and effectiveness of new drugs. The FDA regulations provide:

> "A contention that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is required to be supported by submission of the same quantity and quality of scientific evidence that is required to obtain approval of [a new drug] application for the product, unless FDA has waived a requirement for effectiveness ... or safety, or both ...." (21 C.F.R. § 314.200(e)(1).)

The Agency therefore finds that the products described in subsection (c) which are in compliance with all applicable administrative standards generally pose no significant risk of cancer, and such a finding should be protective of the public

health pending the establishment of specific no significant risk levels.

Two commentators recommended that the Agency delete from subsection (c) the phrase, "[e]xcept as otherwise provided in Section 12705." (Exh. 4, p. 3; C-16, p. 2.) The Agency has concluded that persons attempting to enforce and comply with the Act will enjoy greater certainty regarding compliance where the standards adopted are specific, rather than non-specific. Thus, the Agency is conducting risk assessments for the purpose of adopting permanent specific standards for specific chemicals of concern in food, drug, cosmetic and medical device products. These specific standards will be set forth in section 12705, and when they are adopted will provide a basis for showing that exposures in such products, and other products as well, pose no significant risk. Accordingly, this recommendation was not adopted.

Subsection (d) provides, where a chemical known to the state to cause cancer in a food, drug, cosmetic or medical device is not subject to a specific regulatory level as described in subsection (c), exposure shall be deemed to pose no significant risk if the exposure in which the chemical occurs is in compliance with all applicable administrative standards.

In determining the content of the regulation, the Agency considered the alternative of limiting the regulation to instances where a specific administrative standard had been established as a legal requirement with respect to the permissible level of particular chemical in food, drug, medical device or cosmetic products. The Agency rejected this alternative because it failed to recognize the means by which FDA has implemented and enforced the FD&C Act.

In his August 28, 1987, letter to the Governor, the Commissioner of Food and Drugs stated:

> "Even with regard to substances not affirmatively approved by FDA for foods, drugs, cosmetics or other FDA-regulated products, the agency has adequate procedures for determining their safety and taking necessary regulatory action if problems arise."

In his testimony before the Scientific Advisory Panel, the Commissioner observed that "FDA regulated products are lawfully sold in accordance with federal law do not pose a significant risk to human health" and that "warnings on products that do not pose such a risk are unnecessary, are likely to be confusing, and may be very costly to industry and consumers." The Commissioner made it clear that an FDA decision not to take regulatory action under the general statutory standards in the adulteration provisions of the FD&C Act does not mean that the food is unsafe or poses a significant risk to human health:

"Looking at the food supply as a whole, premarketing approval of chemicals in food is probably more the exception than the rule. For this reason, the absence of an FDA tolerance or other level of concern does not imply that a chemical in a food poses a safety problem. On the contrary, in the usual case it means that no problem has been associated with the chemical in that situation, and given the FDA's broad monitoring of the safety of the U.S. food supply, lack of regulatory action may fairly be viewed as the agency's conclusion that no regulation is needed."

Thus, the lack of a specific FDA level or tolerance does not signify that a chemical may pose a health hazard. FDA devotes its attention to those substances that may be present in potentially unsafe amounts. The absence of an explicit determination is, therefore, a strong indication of over-all safety. As explained by the Commissioner of Food and Drugs, FDA is vigilant to initiate regulatory action whenever new evidence concerning a chemical suggests carcinogenicity or other adverse effects.

The regulatory scheme for medical devices includes not only a system of premarket approval or notification to assure the safety and effectiveness of new devices, FDA requires that medical device manufacturers monitor the safety and effectiveness of all marketed medical devices. (21 C.F.R. part 803.) Manufacturers must report to FDA whenever they receive information that reasonably suggests that a marketed device may have caused or contributed to a death or serious injury, or has malfunctioned in a way that could cause or contribute to serious injury. The purpose of such reports is described as follows:

"These reports will enable FDA to protect the public health by helping to ensure that devices are not adulterated or misbranded and are otherwise safe and effective for their intended use." (21 C.F.R. § 803.1(a).)

The safety of cosmetics is regulated under the existing statutory and administrative standards of the FD&C Act and the Sherman Law. In his testimony, the Commissioner of Food and Drugs states that "Federal regulation of potentially hazardous substances [is] fully sufficient to protect the public health from any significant risks." The Commissioner explained FDA's regulation of cosmetic safety as encompassing premarket approval of color additives used in cosmetics, regulation of some cosmetics as drugs, inspection of cosmetic manufacturing facilities and the banning of hazardous cosmetic ingredients.

As previously noted in the discussion of food regulation, cosmetics only contain color additives that have been approved as safe by FDA. (21 U.S.C. § 376(a).) Use of unapproved color additives or use of approved additives in a manner that does not conform to federal requirements is prohibited by the FD&C Act.

Health and Safety Code section 26701 contains a comparable provision.

In addition to the special safety precautions for color additives previously discussed, FDA regulations impose on manufacturers of cosmetic products the duty to substantiate the safety both of every individual ingredient and of every finished product prior to marketing. (21 C.F.R. § 740.10(a).) Failure to meet this safety requirement causes the cosmetic to be misbranded under FD&C Act section 602(c), unless it contains the following conspicuous statement on the principal display panel: "Warning - The safety of this product has not been determined." FDA regulations also require that the label of a cosmetic product "bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product." (21 C.F.R. § 740.1.)

Accordingly, the Agency concludes that levels of chemicals known to the state to cause cancer, if there are any, in food, drug, medical device or cosmetic products which comply with all applicable administrative standards generally pose no significant risk of cancer. Further, because products which pose no significant risk require no warning under the Act, the public health will be enhanced by these regulations. A proliferation of warnings could effectively prevent the public from determining which hazards are truly important and how personal behavior can impose individual and societal safety, and could lead to cynical disregard for all warnings. In his August 28, 1987, letter to the Governor, Commissioner Young stated FDA's concern that a proliferation of health warnings on FDA-related products "might create serious public health problems" because "the consumer may be confused when confronted by warning labels on large numbers of products and may be less likely to heed those warnings that have been carefully designed by FDA, Congress, and the state to protect against more significant and possibly more immediate harm."

The Agency finds that these concerns are well founded, and that the regulation will prevent this problem by assuring that, where foods, drugs, cosmetics and medical devices contain chemicals listed under the Act, the warnings shall be reserved for levels of chemical exposure that pose a significant risk.

Section 12713 applies only to chemicals known to the state to cause cancer. It does not apply to reproductive toxicants. The "no significant risk" standard of the Act for carcinogens is similar to many standards applied to foods, drugs, cosmetics and medical devices in general. However, existing food, drug, cosmetic and medical device safety law have no equivalent to a "no observable effect" standard that assumes exposure at 1,000 thousand times the level in question. Since there are no existing standards for reproductive toxicants, there is nothing on which a provision similar to section 12713 for reproductive toxicants could be based.

Two commentators noted that subsection (d) refers to subparagraphs 1-8 of subsection (b), not subsection (c). (Exh. 1, p. 3; C-16, p. 3.) It was the intention of the Agency that subsection (d) apply where subsection (c) would not. The reference to subsection (b) was an inadvertent clerical error. This error was corrected in the March 29 proposal.

One commentator recommended that the Agency delete the phrase "[e]xcept as otherwise provided in Section 12705." (Exh. 4, p. 3; C-18, p. 9.) The Agency has concluded that persons attempting to enforce and comply with the Act will enjoy greater certainty regarding compliance where the standards adopted are specific, rather than non-specific. Thus, the Agency is conducting risk assessments for the purpose of adopting permanent specific standards for specific chemicals of concern in food, drug, cosmetic and medical device products. These specific standards will be set forth in section 12705, and when they are adopted will provide a basis for showing that exposures in such products, and other products as well, pose no significant risk. Accordingly, this recommendation was not adopted.

One commentator recommended that, as an alternative to deleting this section, the Agency should clarify that if the state or federal agency responsible for regulating that chemical has admitted inability to assess the level of risk, or alternatively exclude alcoholic beverages from 12713 (d). This commentator contends that the example of urethane in alcoholic beverages proves that not every instance of federal regulatory inaction is tantamount to a determination of no significant risk for purposes of the Act. (C-24, p. 2.)

Implicit in this comment is the belief that, under this regulation, the mere fact that a product is regulated under the FD&C Act, and the FDA has taken no action to prevent the product from being sold, means that the product poses no significant risk. As indicated above, this is incorrect. This section refers to standards only. Every product in each of these categories, including alcoholic beverages, is subject to some kind of administrative standard. In every case there are nonspecific qualitative standards. In many cases there are specific quantitative standards. In order for a product to be deemed to pose no significant risk, it must be in compliance with all applicable administrative standards.

The fact that an administrative agency, such as the federal Food and Drug Administration (FDA), has not taken action against persons causing exposure to a product which is not in compliance with the applicable administrative standards does not mean that the product poses no significant risk. The absence of administrative action may simply mean that the FDA has yet to discover the violation, or that the FDA has, for administrative reasons, decided not to take action. It cannot be taken as conclusive proof that the applicable standards have been met.

It is the intention of the Agency that an action under the Act be available to make certain that these standards are satisfied. Accordingly, the "safe harbor" afforded by this section is available only where all applicable administrative standards have been complied with. Public prosecutors or persons in the public interest may bring actions where such products result in exposures to listed chemicals. The defendant in such an action may prove compliance with all applicable administrative standards and avoid liability. If the defendant cannot show such compliance, then the "safe harbor" is not available, but the defendant may still attempt to prove that there is no significant risk within the meaning of the Act by some other means not reflected in the regulations. Accordingly, adoption of this recommendation does not appear to be necessary.

Section 12721

Section 25249.10 (c) of the Act provides an exemption test for discharges, releases and exposures to chemicals known to the state to cause cancer. The test is whether the person responsible can show that the exposure poses no significant risk "assuming lifetime exposure at the level in question." The Act, however, does not define either "level in question" or "lifetime exposure."

Section 25249.6 of the Act requires a clear and reasonable warning prior to exposure to a listed chemical, and prohibits any discharge, unless this exemption applies. Thus, persons in the course of doing business, in order to avoid violation of the Act, will need to determine the applicability of the exemption prior to exposure, discharge or release. Therefore, they will need to know in advance what will be the assumed or expected "level in question" for purposes of the exemption. They will also need to know what will be the assumed lifetime of the individual exposed for the particular type of exposure.

One commentator contended that the Agency may need to adopt some standards that take into account the unique environs which apartment complexes encompass. (C-22, p. 3.) However, there appears to be nothing unique about apartment complexes. Many products are constructed from components which contain listed chemicals. The manufacturers of these products must also consider whether their finished product will require a warning or poses no significant risk. Accordingly, the Agency at this time adopts no unique standards regarding apartment complexes.

Subsection (a) defines the term "level in question" to mean the chemical concentration of a listed chemical for the exposure in the question, which includes only those exposures for which the person in the course of doing business is responsible. The chemical concentration is usually expressed as micrograms per liter of water, cubic meter of air or gram of food. Because a chemical may exist in a medium of concern due to the acts of some other person, this subsection states what is implied in the Act,

namely, that a person is responsible only for exposures to a chemical that result from her or his acts or omissions.

Since it is not possible to determine in advance what individuals will be exposed by a particular act or omission, and since different individuals enjoy different life expectancies, conventional assumptions must be utilized to promote predictability and consistency in the enforcement of the law. Therefore, subsection (b) defines "lifetime" in the term "lifetime exposure" to refer to a life expectancy of 70 years.

The exemption test of section 25249.10(c) is based upon exposure. It is the "exposure" over the 70 year lifetime which must pose no significant risk "at the level in question". Accordingly, subsection (b) defines "exposure" in the term "lifetime exposure" to mean the "reasonably anticipated rate of exposure for an individual to a given medium of exposure."

The reasonably anticipated rate of exposure will vary from case to case. It may be reasonably anticipated that food will be ingested once each day, or once each week, and so on. What rate of exposure is reasonably anticipated from a given medium, such as a certain type of food or a consumer product, will depend upon the medium, its anticipated use and other circumstances. For example, the publisher of a newspaper using inks containing a listed chemical may not reasonably anticipate that a reader will ingest the Sunday edition, but may reasonably anticipate other contact. A manufacturer of cardboard boxes may not reasonably anticipate the ingestion of a box, but may reasonably anticipate that the box will be used to package food products into which a chemical may migrate. A manufacturer of baby cribs might reasonably anticipate that an infant will chew or teethe on the railings.

One commentator recommended that the Agency make clear that the "reasonably anticipated rate of exposure for an individual to a given medium of exposure measured over a life time of 70 years" shall be the average concentration of the chemical to which the individual may be reasonably anticipated to be exposed over a lifetime of 70 years. (C-39, p. 4.) Any reference to "average concentration", however, appears more closely linked to the definition of "level in question" than the definition of "lifetime exposure." Further, a reference to the average concentration of a chemical to which an individual may be reasonably anticipated to be exposed in a lifetime would appear to make persons responsible for the exposures of others. Such a result is precisely what the second sentence of subsection (a) is intended to avoid. Accordingly, this recommendation was not adopted.

Subsection (c) combines the definitions of "lifetime exposure" and "level in question" into a working formula. The level of exposure which must pose no significant risk assuming lifetime exposure at the level in question is the product of the concentration of the chemical in the medium and the reasonably

anticipated rate of exposure to individuals during a 70-year period to that medium. Under this formula, a certain daily exposure to a chemical in a food product could be calculated, taking into account the concentration of the chemical in the food (in micrograms of chemical per gram of food), and multiplying that concentration times the quantity ingested (in grams of food per day). The product of this multiplication yields the quantity of chemical ingested in that food (in micrograms of chemical per day). This level must not exceed the level derived pursuant to this article.

The rate of exposure to a given medium of exposure is subject to fluctuation. Different individuals take in different amounts of air, water and food. Some may spend considerably more time in an area containing a listed chemical than others. It is, therefore, also necessary to establish certain assumptions about particular media. This is accomplished in subsection (d). However, scientifically more appropriate or specific data may be used where available.

One commentator recommended that exposure assumptions be realistic for the individual substance under consideration. (Exh. 7, Appendix A, p. 14.) Subsection (d) plainly provides that the default assumptions provided may not apply where more specific and scientifically appropriate data are available. Accordingly, the July 29 proposal already addresses this concern.

Paragraph (1) makes assumptions for exposures to the general population. Thus, paragraph (1)A. assumes ingestion of two (2) liters of drinking water per day. Paragraph (1)B. assumes inhalation of twenty (20) cubic meters of air per day. These values are drawn from the Report of the Task Group on Reference Man, published in 1975 by the International Commission on Radiological Protection, and are consistent with assumptions utilized in regulatory toxicology for those media.

One commentator objected that the breathing rate of 20 m^3 is overly conservative, and recommended that 16 m^3 is more realistic. (C-35, p. 13.) This 20m^3 value is drawn from a well-established scientific document and is consistent with assumptions utilized elsewhere in regulatory toxicology. To the extent that the assumption may be conservative, its conservatism is consistent with that displayed in other areas of regulatory toxicology. Thus, it does not appear to be "overly" conservative.

As for whether the assumption is "realistic," the term "realistic" is defined as "tending to or expressing an awareness of things as they really are." (American Heritage Dictionary, Houghton Mifflin Co., 2d College Ed., 1985, p. 1030.) Risk assessors often adopt a conservative approach in order to avoid underestimating the risk. This represents a realistic assessment of the extent of their knowledge. Accordingly, this recommendation was not adopted.

Paragraph (2) provides that different assumptions must be used where the exposure is expected to affect only a subpopulation to which different assumptions properly apply. Certain subpopulations need to be addressed where circumstances involve particular products or environmental conditions which may pose a possible exposure risk to a distinct group of people. For example, pediatric products may be used only by infants. Paragraph (2) provides different assumptions for various subpopulations for the ingestion of water and inhalation of air.

One subpopulation specifically referred to by the July 29 proposal was "mother with conceptus." One commentator recommended that the Agency amend "Mother with conceptus" to read "Woman with conceptus." (C-12, p. 2.) This amendment was made in the March 29 proposal.

Paragraph (3) provides a specific set of assumptions for exposures in the workplace, since workers are normally exposed for only a portion of the day, for a limited number of days each week, for a limited number of weeks per year, and only a portion of the assumed 70-year lifetime. The net result of these assumptions, which are based upon well-accepted conventions, is that occupational exposures posing no significant risk under the Act may involve slightly higher concentrations of the chemical.

It is anticipated that exposures will occur in the workplace to persons other than employees, such as customers, visitors or solicitors. These individuals will probably spend less time in that location as an employee. The Agency believes it is appropriate to differentiate between the potential exposure that may befall a temporary visitor and that of an employee. Therefore, this paragraph assumes such persons will visit the premises one hour per month per 70-year lifetime, and further assumes that they will inhale 1.25 cubic meters of workplace air during each visit.

Paragraph (4) provides assumptions for exposure resulting from the consumption of goods or consumer products as are described in section 12601, subsection (b). The average rate of consumption of the product user, not the per capita consumption of the general population, is the standard. The average rate may be based upon consumption data available for the general category of products. For example, a business packaging corn may rely upon the average amount consumed by persons who eat corn. This approach is more appropriate than allowing each packager to confine his exposure calculation only to his or her market share or the amount of corn he or she packaged, which may be relatively small when compared to the amount consumed by the consumer overall. If it is reasonably anticipated that the product category containing chemical will be ingested only once per week, once per month, or once per year, the resulting intake of the chemical averaged over a daily basis would be 1/7, 1/30, and 1/365 of the value determined when the food is eaten once each day.

Following the July 29 hearing, it became apparent that further clarification to subparagraph (4) would be useful. The reference to the "average rate of intake" could be construed to refer to the average frequency of intake. However, the size of the portion taken in with average frequency could, under the July 29 proposal, be assumed to be the largest portion which could be anticipated. Since the object of this subsection is to establish the rate of exposure which may be "reasonably" anticipated, the Agency concluded that subsection (d)(4) should refer to the average rate of intake for "average users" of a product, not simply "users." Accordingly, the March 29 proposal inserted the word "average" before the word "users" in subsection (d)(4).

One commentator recommended that the regulation clarify that, for product exposures, only exposures of persons to the product of the individual business is to be used in calculating the risk. (Exh. 8, p. 20.) This was not the Agency's intention. The calculation of exposure to a chemical in a consumer product is based upon the reasonably anticipated intake. The reasonably anticipated rate of intake is based upon the degree of exposure to a particular medium. In the case of consumer products, the medium of exposure is the product category, not any particular brand of product. While this may require that calculations assume that an exposed individual will purchase only a single brand or label in a product category, this assumption does not appear unreasonable, since the advertising programs of most businesses aim to achieve exactly that result. Moreover, data about the consumption of a particular brand is not likely to be as readily available to the public as information about overall consumption. Persons in the public interest would need this information to determine whether an enforcement action is warranted. Therefore, this recommendation was not adopted.

One commentator recommended an amendment to allow the Agency to review and approve of generic exposure assessments to alleviate unnecessary enforcement actions in which the Agency would, as in the case of the Safe Use Determination (SUD), render a finding as to the compliance status of those manufacturers attesting to the generic data. (C-37, p. 29-33.) Of course, this could in fact be done under the existing SUD process. The adoption of some additional process appears to be unnecessary.

EXAMPLE OF THE PROCESS

The following example of the risk assessment and exposure assessment process under these regulations is provided for purposes of illustration. This example also utilizes concepts from section 12503 regarding exposure to ambient air and section 12901 regarding methods of detection.

Company X owns an office building and leases space in the building for office purposes. Some of the materials in the building contain asbestos fibers. Company X knows about the presence of asbestos in the building, and knows that some of the asbestos is in a deteriorating condition. For purposes of

discussion, it is assumed that airborne fibers may reasonably be expected as a result of the presence of asbestos in a deteriorating condition, though this may not always occur.

Section 12503, subsection (c) states that an exposure has not occurred if the listed chemical was contained in air that the person received from the ambient air. Hence, if the detectable asbestos fiber concentration inside the building is indistinguishable from the outside asbestos fiber concentration, then there may be no exposure. Further, if scientifically valid monitoring studies indicate that there are diurnal and seasonal fluctuations in asbestos concentrations inside and outside that make it virtually impossible to differentiate between the two, again an exposure may not have occurred. If, however, despite diurnal and seasonal fluctuations, the inside air concentrations frequently exceed the outside air concentrations, then Company X could proceed to compare the increased level to the applicable level posing no significant risk.

This would involve identifying the level posing no significant risk. The Agency has identified that level as 100 asbestos fibers per day, based on a risk assessment performed by the California Department of Health Services (DHS) in a report to the Air Resources Board (ARB) for its Toxic Air Contaminant Program. We know, further, by referring to the DHS/ARB report, published in January 1986 that the 100 fibers are based upon phase contrast microscopy (PCM), which is equivalent to 10,000 to 100,000 fibers, when measured by transmission electron microscopy (TEM). Using an inhalation rate of 20 cubic meters of air per day for the permanent resident, the concentration posing no significant risk is 5 fibers by PCM per cubic meter of air, equivalent to 500-5,000 fibers by TEM per cubic meter of air.

If the increased level in the building exceeds the no significant risk level, the owner should provide a warning to the building's occupants.

Article 8. No Observable Effect Levels

Section 12801

Subsection (a) describes the scientific standards which must be applied to determinations of "no observable effect" within the meaning of the Act. It requires that such determinations be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical. In other words, a showing of no observable effect within the meaning of the Act must be based upon data and protocols which are scientifically valid, sharing a comparable degree of scientific acceptance to the data and protocols which supported the listing of the chemical. The purpose of this provision is to ensure that whatever methods are used to conduct risk and exposure assessments conform to a high standard of scientific validity.

"Safe Harbor" Concept

Subsection (a) also provides that nothing in Article 8 is intended to preclude the use of evidence, standards, assessment methodologies, principles, assumptions or levels not described in the article to establish that an exposure would have no observable effect. Therefore, the methodologies, data, principles, assumptions and levels described in the sections following section 12801 are not exclusive and do not prevent a plaintiff or defendant in an enforcement action from establishing "no observable effect" by other means. However, such a showing must be based upon data, standards, methodologies, principles and assumptions which are scientifically valid, as provided in the first sentence of subsection (a).

A similar approach was adopted by the Agency in its regulation regarding "clear and reasonable warnings." (22 C.C.R., § 12601.) That section provided minimum standards in order for warnings to be clear and reasonable, and provided "safe harbor" methods and messages which are deemed to be clear and reasonable, but also provided that the provision of the "safe harbor" methods and messages should not be construed to preclude a person from providing warnings in any other clear and reasonable fashion. Similarly, this article establishes a minimum requirement that the evidence and standards used are of comparable scientific validity to the evidence and standards supporting the listing of the chemical. "Safe harbor" levels and methodologies deemed to have no observable effect within the meaning of the Act are provided. However, a person is permitted to use any data, standards or assessment methodology, or apply any assumptions or principles desired to show that an exposure would produce no observable effect assuming exposure at one thousand times the level in question. Where a "safe harbor" level or methodology is not used, it remains a question of fact in any enforcement action whether the exposure poses would produce no observable effect within the meaning of the Act.

The July 29 proposal referred only to a person's use of evidence, standards or levels not described in Article 8 as a means of proving no observable effect within the meaning of the Act. In

reviewing the comments to the July 29 proposal, it became clear that reference also needed to be made to risk assessment methodologies, principles and assumptions, since many commentators took this omission to signifiy that the risk assessment methodology, principles and assumptions expressed in section 12803 are mandatory. The Agency intends that section 12803 provide a "safe harbor" methodology, but does not necessarily represent the only method by which a person may determine a level of exposure which would produce no observable effect within the meaning of the Act. Accordingly, the March 29 proposal added specific reference to risk assessment methodologies, principles and assumptions.

Subsection (b) of section 12801 provides a menu of the "safe harbor" methods for determining no observable effect levels set forth in the regulations. The Agency has recognized in this article three alternative routes for arriving at a "no observable effect" level. Subsection (b) is intended to afford persons enforcing the Act and persons in the course of doing business an easy reference to the use of the "no observable effect" level regulations which follow section 12801.

Generally, a determination of a "safe harbor" level producing no observable effect within the meaning of the Act may be made (1) through the performance of an assessment in accordance with principles set forth in section 12803, (2) the application of specific "no observable effect" levels set forth in the regulations or (3) the application of a regulatory level set forth in state or federal law derived from an assessment substantially equivalent to the assessment described in section 12803, and which establishes a maximum allowable daily dose level in the manner provided in this article.

The July 29 proposal had provided:

> The determination that exposure to a listed chemical has no observable effect for purposes of Health and Safety Code section 25249.10(c) may be made under this article by . . . ."

The following subparagraphs listed the means by which a "safe harbor" determination could be made. In order to clarify that Article 8 is intended to provide "safe harbors" and not binding levels and methodologies, the March 29 proposal amended this first clause of subsection (b) to read:

> "A level of exposure to a listed chemical shall be deemed to have no observable effect, assuming exposure at one thousand times that level, provided that the level is determined: . . . ."

Throughout the article the term "NOEL" is used to refer to the no observable effect level (i.e., the maximum dose level at which a chemical has no observable reproductive effect). Subdivision (c) defines this reference. It is implicit from the Act that the observable effects of concern are <u>reproductive</u> effects, not <u>any</u> observable effect. However, one commentator recommended that the regulation make clear that a NOEL for purposes of the Act relates

to a reproductive toxicity endpoint, not to a general toxicity endpoint. (C-44, p. 9.) The July 29 proposal did not specifically refer to this distinction. Accordingly, the March 29 proposal makes clear that the observable effects of concern are reproductive effects.

Two commentators recommended that the regulation limit the definition of NOEL to no observable adverse reproductive effect. (Exh. 8, p. 21; C-20, p. 5.) The difficulty with this recommendation is that the Act refers to "no observable effect," not "no observable adverse effect." Further, adoption of the term "adverse" would then require further definition, since reasonable minds could differ on whether a particular effect is adverse or benign.

One commentator recommended that the regulation specifically provide that the failure to establish a no observable effect level for a reproductive toxicant does not mean that it in fact does have an observable effect at all levels and under all conditions. (Exh. 7, p. 61.) The July 29 proposal did make such a provision in Article 7 dealing with carcinogens. Upon further review, there appears to be no reason why a similar provision could not be made for reproductive toxicants. Accordingly, the March 29 proposal added an new subsection (d) to section 12801 which provides:

> "(d) The chemicals specifically contained in this article do not include all listed reproductive toxicants for which there is a level of exposure which has no observable effect assuming exposure at one thousand times the level in question. The fact that a chemical does not specifically appear in this article does not mean that it has an observable effect at any level."

Similarly, the July 29 proposal provided in Article 7 that the article established exposure levels solely for purposes of the Act. Again, there appears to be no reason why a similar provision could not be made for reproductive toxicants. Accordingly, the March 29 proposal added an new subsection (e) to section 12801 which provides:

> "(e) This article establishes exposure levels solely for purposes of Health and Safety Code section 25249.10(c). Nothing in this article shall be construed to establish exposure levels for other regulatory purposes."

Section 12803

This section provides a methodology for conducting quantitative risk assessments for the purpose of establishing a "safe harbor" for no observable effect levels which assume exposure at one thousand times the level in question. There are many reasons why it is important to have such guidelines in these regulations. For many chemicals, levels of exposure, discharge or release which would produce no observable effect within the meaning of the Act may not have been established either for purposes of the Act or other regulatory programs. Thus, persons in the course of doing business involving the chemicals may not be able to

determine whether they are in compliance with the Act. As a result, such businesses may unnecessarily alter their business practices, or provide unnecessary warnings which may dilute the effectiveness overall of warnings under the Act. Finally, some persons in the course of doing business may disagree with the specific levels which have been established because, for example, they may believe that the established level was derived from data which is outdated. These persons may choose to conduct their own risk assessments to ascertain the appropriate level producing no observable effect.

There are many variables in the performance of a risk assessment. Although the Act eliminates one variable, since it imposes a mandatory one thousand-fold uncertainty factor, there are often several studies or sets of data of varying quality upon which the assessment may be based. There are a variety of assumptions which may need to be applied. By selecting data of high quality, choosing more conservative and accepted assumptions, persons in the course of doing business should be able to calculate "no observable effect" levels which could easily withstand challenge. However, persons enforcing the Act and persons in the course of doing business may be motivated to base their analyses upon less reliable data and less accepted or more controversial assumptions to suit their immediate purposes and objectives.

The purpose of this section is to provide a collection of principles for the conduct of risk assessments which will, if observed, produce a "no observable effect" level which is conservative, reliable and consistent with the purposes of the Act and which the Agency may reliably conclude would produce no observable effect assuming exposure at one thousand times the level in question. This section is not designed to require that these assumptions and principles be applied to all assessments used when proving no observable effect within the meaning of the Act. Persons may conduct risk assessments in any manner they choose. However, in order for a risk assessment to provide a "safe harbor" level, it must be conducted in accordance with this section.

"Safe harbor" risk assessments need not be performed in a rigid fashion. Rather, it is intended that each default assumption or principle set forth in section 12803 apply only in the absence of a scientifically more appropriate principle or assumption.

Subsection (a) requires that all risk assessments intended to establish a "safe harbor" no observable effect level within the meaning of the Act be based upon evidence and standards of comparable scientific validity to the evidence and standards which formed the basis for the listing of the chemical. The listing of chemicals under Health and Safety Code section 25249.8 (b) must be based upon "scientifically valid testing according to generally accepted principles." Therefore, the same standard applies to the performance of risk assessments used to support a showing of "no observable effect."

The subsection also provides:

"A quantitative risk assessment which conforms to this

> section shall be deemed to determine the level of exposure to a listed chemical which has no observable effect, assuming exposure at one thousand times the level in question."

Following subsection (a) are principles and assumptions which must be observed, absent a more appropriate assumption or principle,in order to obtain a "safe harbor" result.

The July 29 proposal did not expressly provide that observing the described methodology would produce a result "deemed" to produce no observable effect. This prompted one commentator to object to subsection (a), contending that default factors are even less appropriate for reproductive toxicants than for carcinogens since the statute specifies a safety factor at a maximum level to adjust for any uncertainties caused by use of particular assumptions, and recommended that the default assumptions either be deleted, or the second sentence be revised to provide:

> "In the absence of other scientifically appropriate principles or data that meet these criteria, the following default assumptions may be considered if they meet these criteria and are appropriate for the particular chemical and data in question: . . . ." (Exh. 8, p. 22-23.)

It was clear from this comment that the status of the risk assessment methodology described in section 12803 as a "safe harbor" only was not well delineated in the July 29 proposal. Accordingly, the March 29 proposal amended section 12801(a) to specifically provide that no observable effect within the meaning of the Act can be proven on the basis of risk assessment methodologies, principles and assumptions other than those described in section 12803. Such a risk assessment would not provide a "safe harbor," but is nevertheless available in the event of an enforcement action. Whether such an assessment in fact proves no observable effect within the meaning of the Act would be a question for the court to decide.

In order to clarify that the default, or scientifically more appropriate, assumptions and principles are required only for "safe harbor" assessments, the March 29 proposal amended subsection (a) to reflect the language shown above. The Agency believes that, in conjunction with the March 29 amendment to subsection 12801(a), the regulation now clearly provides that the default assumptions need not be used in all assessments of no observable effect within the meaning of the Act.

The July 29 proposal further provided that the default principles and assumptions "should be considered." One commentator recommended that the default assumptions consistently be described as principles that "should" be considered, and recommended the substitution of the word "should" wherever the word "shall" is used, as in subparagraphs (a)(4), (a)(5), and (a)(6). (Exh. 7, p. 62.) However, use of the word "should" implies that assumptions and principles other than the default assumptions and principles may be used even in the absence of more appropriate assumptions and principles. To allow any

assumption as an alternative to the default assumptions or principles could erode the certainty which the Agency requires in order to deem that a level would produce no observable effect within the meaning of the Act. Accordingly, the March 29 proposal did the opposite of this recommendation. References to the word "should" were changed to "shall." Thus, whenever the "safe harbor" methodology is employed, the default assumptions and principles, or scientifically more appropriate assumptions and principles, must be used.

This same commentator objected post-hearing to the deletion of the requirement that the default assumptions or principles "should be considered," and its replacement with "shall apply." (P-1, p. 6.) Again, section 12803 provides a "safe harbor" methodology which is designed to produce a result which the Agency can be assured will produce no observable effect within the meaning of the Act. In order to maintain this level of assurance, it is essential that the described methodology not only be considered, but in fact be applied. Further, as the commentator points out, there is no requirement that the "safe harbor" methodology be used. Accordingly, the amendment has been retained.

One post-hearing commentator expressed its concern that the first sentence of section 12803(a) could be read to mean that a level derived from a risk assessment under section 12803 is the only allowable no observable effect level. (P-11, p. 3.) This was not the Agency's intention and represents too confined an interpretation of the regulation. As section 12801(b) makes clear, a level of exposure to a listed chemical shall be deemed to produce no observable effect within the meaning of the Act provided that it satisfies one of the enumerated sections. As section 12801(a) further makes clear, nothing in article 8 shall preclude a person from using risk assessment methodologies or levels not described in article 8 to establish that a level of exposure to a listed chemical would produce no observable effect within the meaning of the Act. Plainly, section 12803 was intended to provide a methodology to derive a "safe harbor" level only, not a binding number for all purposes.

One post-hearing commentator recommended that the reference to "principles or assumptions scientifically more appropriate" be changed to "equally or more appropriate." (P-1, p. 6.) Arguably, this does not constitute a comment on a post-hearing change, since the requirement that alternative assumptions and principles be more scientifically appropriate was contained in the July 29 proposal. The commentator's failure to make its objection during the comment period to that proposal forecloses any objection at this stage of the regulatory process, and the Agency is not obligated to respond to the comment.

Nevertheless, the Agency points out that the "safe harbor" methodology in this section is designed to provide a result which the Agency can with assurance conclude would produce no observable effect within the meaning of the Act. In order to maintain this level of assurance, the Agency believes that it is necessary to require that alternative assumptions or principles be more appropriate. The commentator complains that it may be

difficult to prove that another principle or assumption is "more" appropriate than the default. The Agency can find nothing difficult with this burden. It simply entails a showing that there is a scientific basis for concluding that the default assumption or principle is less appropriate in a particular situation, and that an alternative assumption or principle is more appropriate. Accordingly, this recommendation was not adopted.

Default Assumption and Principles

Paragraph (a)(1) provides that only studies producing the reproductive effect which formed the basis for the listing of the chemical shall be used for determining the "safe harbor" NOEL. The Panel has determined that a number of reproductive effects come within the meaning of "reproductive toxicity" including, in females, menstrual disorders, infertility, spontaneous abortion, genetic damage, adverse effect on gonadal function, adverse effects on conception and maternal complications. In males, the effects include impotence, semen quality changes, genetic damage, and adverse effects on gonadal function. For the conceptus, the effects include embryonal or fetal toxicity, birth defects, neurodevelopmental abnormalities, transplacental carcinogenesis, genetic damage, stillbirth, and functional or developmental changes.

When recommending a reproductive toxicant for listing pursuant to section 25249.8 of the Health and Safety Code, the Panel relies upon data demonstrating that particular types of reproductive toxicologic effects in humans or animals, in males, females, or the developing young, result from exposure to the chemical. Inasmuch as the chemical is listed for a particular effect, it follows that studies producing this effect should be utilized to determine the dose level at which the effect will no longer be observed. Therefore, subsection (a)(1) provides that only such studies should be used for purposes of the "safe harbor" level.

One commentator objected that, to conduct an assessment and determine a NOEL, it is necessary to know the evidence, standards and reproductive effects which provide the basis for the determination that a chemical is known to the state to cause reproductive toxicity. The commentator contended, as an example, that there is no way to know the reproductive effects for which lead was listed. Thus, the commentator recommended that the regulations should provide a complete description of the specific reproductive effects as well as a description of the studies, evidence, and scientific standards known to the State and which formed the basis for listing a chemical as a reproductive toxicant, either in the regulations themselves, or in a separate available document. (C-20, p. 9.) It should not be difficult for a person or organization sophisticated enough to perform a risk assessment to determine the reproductive effects for which a chemical has been listed as known to the state to cause cancer or reproductive toxicity. There are several ways to make this determination. Section 12000 sets forth the list of chemicals known to the state to cause cancer or reproductive toxicity. The listing of the reproductive toxicants is divided into three subgroups: (1) developmental toxicity, (2) female reproductive

toxicity, and (3) male reproductive toxicity. Thus, in conducting the risk assessment, a person needs only to consult the list to determine which effects provide the basis for the listing.

If more specific information is desired and the chemical was listed based upon the recommendation of the SAP, the person may consult the transcript of the hearing of the SAP or data provided to the SAP by the Agency and other interested parties to determine the specific reproductive effect of concern. This information may be obtained from the Agency. If a chemical, such as lead, ethylene oxide or 1,2 dibromo-3-chloropropane (DBCP), was listed under the Act based upon its prior listing as a known human reproductive toxicant within the scope of the federal Hazard Communication Standard (HCS), then the reproductive effects for which it was listed under the Act are the same as the effects which brought it within the scope of the HCS. A more specific understanding of the reproductive effect of concern could be obtained through a review of the federal register to determine the basis for the HCS reference.

In any event, Article 8 does not appear to provide the appropriate part of the regulations to set forth information related to the listing of the chemical. That amendment, if needed, would more appropriately be set forth in section 12000 (22 C.C.R., 12000). Accordingly, this recommendation was not adopted.

One commentator recommended that the references to reproductive effect refer to reproductive effects "at levels which do not produce maternal toxicity." (Exh. 1, p. 3.) Maternal toxicity is simply one of many factors to be taken into account when evaluating data to determine whether it provides a basis for assessing the developmental toxicity of a chemical. It does not appear necessary to specifically mention this factor or any other. Specific mention of this factor, which applies in the evaluation of developmental toxicity, might suggest that the concept of the NOEL applies only where developmental toxicity is involved. Accordingly, this recommendation was not adopted.

There will be cases in which a chemical is listed because it produces multiple reproductive effects, each with its own "no observable effect" level. There appear to be three alternatives to choosing the applicable "no observable effect" level for purposes of the Act in such circumstances. First, the level could be based upon studies producing the effect having the lowest "no observable effect" dose level. Second, separate levels could be established for each observable effect. Third, the level could be based upon the combined results of the studies producing the reproductive effects for which the chemical was listed. However, this latter would be more in the nature of an "average observable effect" level, not a NOEL, and there appears to be no scientific basis for such an approach. Since most exposures are directed at the general population, rather than specific subpopulations, separate NOELs for each observable effect generally would produce little benefit. Accordingly, the simpler approach is to base the NOEL on the result observed in the most sensitive population. Where the exposure is directed at

a specific subpopulation, the application of a different NOEL may be appropriate.

Paragraph (a)(2) provides that epidemiologic data sets used for quantitative assessments must conform to generally accepted scientific principles, such as the selection of the exposed and reference groups, the reliable ascertainment of exposure, the completeness of follow-up, and the identification and quantification of confounding factors. These examples are offered for purposes of illustration, and are not intended as a limitation. The intended purpose of this provision is to assure that the data upon which risk assessments are based is of high quality.

One commentator recommended that, because of the mandatory 1000-fold uncertainty factor, the regulations should allow NOELs to be based solely on animal exposure studies, and exclude human studies, which might warrant a lower uncertainty factor. Otherwise, this commentator argued, the regulated community may be encouraged to withhold information derived from actual human exposure. (C-20, p. 22.) In effect, this commentator is suggesting that the Agency should permit "safe harbor" assessments to be based upon potentially inappropriate science in order to partially circumvent the express requirement that exemption from the Act be available only at levels which produce no observable effect assuming exposure at one thousand times the level in question. This does not appear to be authorized.

Paragraph (a)(3) makes provisions similar to paragraph (a)(2) applicable to animal bioassay studies. Again, the factors of data selection specified in the paragraph are offered for purposes of illustration, and are not intended as a limitation.

Paragraph (a)(4) provides that the analysis should be based upon the most sensitive of the studies which, under paragraphs (a)(2) and (a)(3), are deemed to be of sufficient quality. Because of the wide range of sensitivity to chemicals observed in humans, it is likely that the response of the most sensitive study will be representative of the response of some individuals. In the absence of a scientifically more appropriate assumption, basing analysis on the most sensitive study will provide a greater level of protection to humans.

One commentator objected that the most sensitive study may not be indicative of the likely human response, and recommended that this paragraph be amended to read: "The NOEL should be based on the most appropriate study deemed to be of sufficient quality." (C-36, p. 6.) However, if it is scientifically more appropriate to base the assessment on a study other than the most sensitive one, this may be done and the "safe harbor" effect of the result preserved. Therefore, it does not appear necessary to adopt this recommendation.

Paragraph (a)(5) provides that the result obtained from the most sensitive study shall be applicable to all routes of exposure, except those routes for which the results are irrelevant. Data on the reproductive toxicity of a chemical to both humans and animals are not always available for a particular chemical and

route of exposure. The inherent physical characteristics of the chemical in question may dictate a particular study protocol. Therefore, it may be necessary to utilize experimental results from one route of exposure for purposes of another.

Absent studies demonstrating a relationship between different routes of administration and differences in reproductive response by those routes, it is more appropriate to assume that a chemical that produces an an observable adverse reproductive effect by one route, such as ingestion, is also toxic to reproductive functions by other routes, such as inhalation, and vice versa.

Absorption studies may reveal that a chemical administered by a particular route will be poorly absorbed. If according to generally accepted principles data obtained from such an exposure route are irrelevant to exposures by other routes, this assumption may yield and a different data set may be more appropriate. However, when scientifically based interpretations of these data are able to allow predictions of exposure by other routes, the assumption should apply and the data ought to be utilized.

One commentator recommended that paragraph (a)(5) be amended to read: "If the results obtained from the most appropriate study deemed to be of sufficient quality indicate an observable effect, the results of the study shall only be applicable to those exposure routes which were the subject of the study." (C-36, p. 6.) In effect, the adoption of this recommendation could result in a level inapplicable to the exposure for which the level was developed. The Agency believes that greater flexibility is desirable.

Paragraph (a)(6) allows the use of physiologic, pharmacokinetic and metabolic considerations in the assessment, where such data may be taken into account with confidence. The susceptibility of different animal species to a given chemical may vary due to differences in metabolism and pharmacokinetics. Certain chemicals are known to cause adverse reproductive outcomes in some test species but not humans because of differences in anatomy, physiology, metabolism, and other factors. For example, the placenta is distinctive from that of primates, and chemical behavior distinct to the rodent placenta may not necessarily be similar properties in primates. This provision allows the use of such data to explain scientifically differential responses among animal species when determining the relative sensitivity of humans. However, the data must be of sufficient quality that it may be taken into account with confidence.

Paragraph (a)(7) provides that, where testing produces an observable effect, but the data does not establish a dose level producing no observable effect, the lowest observable effect level (LOEL) should be divided by 10 to produce an assumed NOEL. The practice of dividing a LOEL by an uncertainty factor in order to predict a NOEL is common among regulatory agencies, such as DHS, and will facilitate the establishment of NOELs where circumstances would otherwise prevent their development.

Subsection (b) provides for the conversion of the NOEL to a daily human dose level. Under paragraph (a)(1) the NOEL is to be expressed in terms of milligrams per kilogram of body weight per day. Subsection (b) accomplishes this conversion by multiplying the daily dose per kilogram by the assumed body weight of the affected population. Thus, when the reproductive effect is upon the male, a 70-kilogram body weight is assumed. When the effect is upon the female or the conceptus, the assumed body weight is 58 kilograms. These assumed body weights are derived from the Report of the Task Group on Reference Man, published in 1975 by the International Commission on Radiation Protection. The use of assumed body weights permits persons in the course of doing business to determine in advance whether the levels involved in their activity will produce no observable effect in the exposed population.

The adult female body weight is used where the reproductive effect is upon the conceptus (i.e., the developing child) because the human maternal exposure is the vehicle for exposure to the conceptus, and because it parallels the situation in animal experimentation, where test doses are given to the pregnant animal, based on its body weight.

By observing the methodology described in section 12803, a person can calculate a "safe harbor" no observable effect level. The Act further requires that exposures to reproductive toxicants not exceed one one-thousandth of the no observable effect level in order to be exempt from the warning requirement and the discharge prohibition of the Act. Thus, the "safe harbor" no observable effect level must be further divided by 1000 in order to determine the level which will be deemed exempt under the Act.

Section 12805

Subsection (a) provides that exposure to a level of a listed chemical at or below the level set forth for the chemical in subsection (b) produces no observable effect within the meaning of the Act. The purpose of this section is to set forth "no observable effect" levels established for purposes of the Act in order to provide a "safe harbor" for those who might have difficulty identifying such levels if left to their own devices.

The establishment of specific levels is necessary. Most businesses do not have the resources to conduct their own risk assessments, whether or not under the principles of section 12803. Yet each business with ten or more employees needs the ability to determine whether its activities comply with the Act, require a warning, or require change. If the Agency did not establish specific levels, these businesses might have no way of making this determination.

Subsection (b) provides levels for two chemicals known to the state to cause reproductive toxicity: ethylene oxide and lead. Both chemicals are identified by the federal Occupational Safety and Health Administration (OSHA) as known human reproductive toxicants based upon evidence of their effects on humans, and this resulted in their inclusion on the Governor's initial list pursuant to section 25249.8 (a) of the Act.

The difficulty in identifying a NOEL for reproductive toxicants when the effects of concern are based upon human experience rather than animal bioassays is that there is often no precise data predicting what levels will produce no observable effect. However, there is experience derived from the occupational setting which suggests that exposure to certain regulated levels does not produce the reproductive effect of concern. Hence, the Agency has utilized certain limits for occupational exposures as surrogates for the NOEL in the workplace. The levels set forth in subsection (b) represent one one-thousandth of the occupational exposure limits. This approach is consistent with the purposes of the Act.

Lead

The OSHA-permissible exposure limit for lead is 50 micrograms per cubic meter of air. One can calculate a daily exposure, as described above, of 500 micrograms per day. Dividing by 1,000 in this case yields an allowable level of 0.5 microgram of lead per day.

Informal pre-notice comments from some interested parties utilized different methods to identify the allowable levels for lead. One party utilized blood lead levels, as indicators of male reproductive toxicity, and found an allowable level of 0.7 micrograms of lead per day, close to the Agency's value. However, the Agency declined to identify 700 micrograms of lead per day, which is considerably higher than the occupational exposure limit, as a level that would result in no observable reproductive effect.

Another pre-notice commentator utilized an animal-derived NOEL, and identified an allowable level of 37 micrograms of lead per day, a value that would require the Agency to accept 37,000 micrograms per day as a level that would result in no observable reproductive effect. Clearly, that would be inappropriate, since that level would exceed the occupational limit by nearly 100-fold.

Several commentators at the hearing objected generally to the "safe harbor" lead level, pointing out that the 0.5 microgram per day level does not provide a "safe harbor" that many can comply with. (C-16, p. 3; Exh. 6, p. 8-9; C-40, p. 12.) The purpose in setting this level, however, is to establish a level of exposure which the Agency can be certain is in fact safe within the meaning of the Act. The fact that some businesses may not be able to comply with the level does not appear to conflict with this purpose. Persons are not bound by any level set in this section, and may prove that no observable effect would result at a higher level in the event of an enforcement action.

Comments similar to those made prior to the notice were made during the 45-day comment period. Several commentators recommended that lead agency reconsider its approach to establishing a NOEL for lead, and that it either raise the NOEL on the basis of animal-derived studies or eliminate altogether the specific regulatory level for lead in Section 12805(b).

(Exh. 6, p. 9; C-21, pp. 8-10; C-38, p. 10; C-44, p. 2.) Specifically, these commentators recommend that the level be set at 35 micrograms/day. It was argued that a review of the human data does not support an association between low-level lead exposure and long-term stable deficits that would allow derivation of a NOEL for developmental toxicity, that animal studies provide an appropriate basis for quantitative risk assessment, that the overall NOEL for lead, based upon animal studies, ranges from 0.6 to 0.9 mg/kg/day, and that using the NOEL range arrived at for the most sensitive endpoint (female reproductive effects) in animal studies as reported by Kimmel et al. (1980), the resulting regulatory lead level should range from 35 to 52 ug Pb/day, with the 1000-fold safety factor.

Since the exemption under the Act requires there be no observable reproductive effect at one thousand times the level in question, it is instructive to evaluate these commentator's alternative level from that perspective. A level set at 35 micrograms would mean that an exposure of 35,000 micrograms would have no observable effect. These commentators apparently feel that such a result would be appropriate for developmental toxicity.

Lead is a reproductive toxicant, however, for males and females as well as in developing infants. As stated by OSHA:

> "chronic overexposure to lead impairs the reproductive systems of both men and women. Overexposure to lead may result in decreased sex drive, impotence, and sterility in men. Lead can alter the structure of sperm cells raising the risk of birth defects. There is evidence of miscarriage and stillbirth in women whose husbands were exposed to lead or who were exposed to lead themselves. Lead exposure also may result in decreased fertility, and abnormal menstrual cycles in women . . . ." (29 C.F.R. § 1910.1025.)

> "Prevention of adverse health effects for most workers from exposure to lead throughout a working lifetime requires that worker blood lead (PbB) levels be maintained at or below forty micrograms per one hundred grams of whole blood (40 micrograms/100 grams). The blood lead levels of workers (both male and female workers) who intend to have children should be maintained below 30 micrograms/100 grams to minimize adverse reproductive health effects to the parents and the developing fetus." (Id.)

Hence, considering 30 micrograms/100 grams to be a functional equivalent reproductive NOEL, OSHA identifies that level to be 75 percent of the blood limit targeted by the permissible exposure limit (PEL).

OSHA further reports the occurrence of teratospermia at mean blood lead levels of 53 micrograms/100 grams and hypospermia and asthenospermia at 41 micrograms/100 grams.

If the inhalation PEL of 50 micrograms per liter per day for 8 hours (10 cubic meters of air) leads to 500 micrograms per day

a level which should keep the PbB below 40 micrograms/100 grams of blood, it can be extrapolated that the anticipated blood levels likely to result from an exposure of 35,000 micrograms per day, as suggested by the commentators, would result in a PbB of 2800 micrograms/100 grams, a level which not only would produce observable effects, but would likely be incompatible with human existence. Accordingly, this recommendation was not adopted for purposes of the "safe harbor" level.

One commentator objected that the "safe harbor" lead level improperly assumes that PELs are established without allowance for any safety factor. (Exh. 6, p. 8.) As indicated above, considering 30 micrograms/100 grams to be a functional equivalent reproductive NOEL, OSHA identifies that level to be 75 percent of the blood limit targeted by the permissible exposure limit (PEL). This observation does not seem to support the many-fold safety factor which the commentators viewed as being applied in the workplace standard.

Another commentator compared the "safe harbor" lead level in the regulation to EPA drinking water level of 50 micrograms, EPA's proposed level of 20 micrograms, and World Health Organization level of 100 micrograms. (Exh. 6, p. 7.) Similarly, another commentator recommended that EPA's proposed, revised maximum contaminant level (MCL) for lead be substituted for the current NOEL lead level listed in Section 12803. (C-40, p. 13.) However, EPA's proposed MCL does not include a 1000-fold safety or uncertainty factor. Thus, the EPA level would be inappropriate for purposes of the Act. Nor do these other agencies necessarily apply safety or uncertainty factors of the same magnitude as required by the Act. Therefore, it should come as no surprise that a "safe harbor" level under the Act may be more restrictive than levels with which people are familiar.

Two commentators objected that the "safe harbor" lead level is based upon inhalation, not ingestion, since the lead PEL which the Agency divided by one thousand is an ambient air standard. These commentators observed that lead absorption into the bloodstream from air inhaled into the lungs approaches 50 percent, while absorption from ingestion is only 10 percent. (See U.S. EPA, Air Quality Criteria For Lead, EPA/600/8-83/028bf (June 1986).) Therefore, they objected that different levels were not provided for different routes of exposure. (Exh. 6, p. 8; C-40, p. 12.)

It does not appear necessary to adopt a separate number for each possible route of exposure. If there is scientifically valid absorption data showing that a chemical is absorbed to a lesser extent by one route than another, then a person may utilize that data to show that exposure by the route of poor absorption would produce no observable effect. Section 12801 specifically provides that persons may utilize levels other than those set forth in this article.

One commentator recommended that, since the 1000-fold safety factor is built into the statute, the lead agency should modify its approach to determining the NOEL. (Exh. 6, p. 8.) In effect, this commentator is suggesting that a higher NOEL be

created in order to allow a higher "safe harbor" exposure level. The Agency does not believe that this would be consistent with the Agency's purpose in adopting this regulation.

Ethylene Oxide

The permissible exposure limit for ethylene oxide, as identified in Title 8, California Code of Regulations, General Safety Orders, is 2,000 micrograms per cubic meter of air. One can calculate a daily exposure, based on a workplace inhalation rate of 10 cubic meters of air inhaled per day, of 20,000 micrograms per day. Dividing by 1,000 yields an allowable level of 20 micrograms of ethylene oxide per day.

Several commentators objected that the ethylene oxide level is too low as well. One commentator observed that the actual NOEL in studies supporting the PEL is 30 times higher than the PEL, and recommended that actual OSHA NOELs be used. (Exh. 4, p. 4; C-8, p. 2; C-18, p. 14.) Ethylene oxide (EtO) was listed as a reproductive toxicant based upon known human effects. Hospital workers have been shown to be at risk of spontaneous abortion associated with EtO sterilization of surgical instruments. (R. Hemmilci et al., British Medical Journal, Vol. 285, 20 Nov 1982, p. 1461.) The Agency views the occupational limits for EtO to be an appropriate surrogate for a human NOEL at this time, given the human effects. In view of the discussion surrounding the lead level, there appears to be little safety margin between occupational limits and the level of reproductive concern. In any event, persons may not wish to utilize the safe harbor provided in this section. Clearly, a person may use whatever proof is available to establish that a level poses no observable reproductive effect at 1000 times the level in question. Accordingly, the level set for EtO was retained.

Three commentators recommended that the Scientific Advisory Panel (Panel) be required to review all NOELs. (Exh. 4, p. 5; Exh. 8, p. 17; C-38, p. 8.) However, questions of no observable effect generally do not involve the extensive extrapolation issues relevant to carcinogens. The applicable uncertainty factor is fixed in the statute. Therefore, there does not appear to be the same need for review by the SAP.

One commentator recommended that the Agency amend Article 8 to contain a provision comparable to proposed section 12707(a) for listing chemicals that have no observable effects by specific routes of exposure. (Exh. 7, p. 62.) The Agency is unaware that any of the listed reproductive toxicants would satisfy the requirements of a provision comparable to section 12707(a). Until such time, there does not appear to be any basis for adopting such a provision.

One commentator recommended that article 8 include a provision similar to section 12709 for trace elements. (Exh. 8, p. 23.) However, only elemental lead might satisfy such a provision. The Agency has already adopted a specific level for lead for purposes of the Act. The Agency is unaware that any of the other listed reproductive toxicants would satisfy such a provision. Thus there appears to be no basis for adopting such a provision.

One commentator recommended that the regulation should establish a presumption that foods which contain listed reproductive toxicants produce no observable effect so long as they are regulated by and in compliance with state and federal food safety laws. (C-16, p. 3.) Similar recommendations were made for over-the-counter drugs (Exh. 2, p. 13.) and medical devices (Exh. 4, p. 4.) Of course, the Agency has never contended that the mere regulation of a commodity exempted it from the Act. As for compliance with existing safety laws, the Agency is unaware that the Federal Government in the regulation of these products, necessarily applies to no observable effect levels an uncertainty factor of one thousand. Accordingly, these recommendations could not be accepted.

Section 12821

Section 25249.10(c) of the Act provides an exemption test for discharges, releases and exposures to chemicals known to the state to cause reproductive toxicity. The test is whether the person responsible can show that the exposure would have no observable effect "assuming exposure at one thousand (1,000) times the level in question." The Act, however, does not define "level in question."

Section 25249.6 of the Act requires a clear and reasonable warning prior to exposure to a listed chemical, and section 25249.5 prohibits any discharge, except where this exemption applies. Thus, persons in the course of doing business, in order to avoid violation of the Act, will need to determine the applicability of the exemption prior to exposure, discharge or release. Therefore, they will need to know in advance what will be the assumed or expected "level in question" for purposes of the exemption.

Subsection (a) defines the term "level in question" to mean the chemical concentration of a listed chemical for the exposure in question, which includes only those exposures for which the person in the course of doing business is responsible. The chemical concentration is usually expressed as micrograms per liter of water, cubic meter of air, or gram of food. Because a chemical may exist in a medium of concern due to the acts of some other person, this subsection states what is implied in the Act, namely, that a person is responsible only for exposures to a chemical that results from her or his acts or omissions.

One commentator recommended that the regulation provide guidance for determining the chemical concentration of a listed chemical, since the level of a listed chemical in a product may fluctuate from unit to unit of production, and specifically recommended that it refer to "level in question" as the mean or average level of a listed chemical unless exposure to the listed chemical produced acute adverse reproductive effects as the result of a brief period of exposure. (C-20, p. 13.) The Act does not appear to provide a basis for such a distinction. It does not distinguish between reproductive toxicants on the basis of their acute or chronic toxicity. It simply provides that the "level in question" must be one thousand times less than the level which

would produce no observable effect. A consistent interpretation of the words "level in question" appears to be much less confusing and more consistent with the Act. Accordingly, this recommendation was not adopted.

The exemption test of section 25249.10(c) is based upon exposure. It is the "exposure" which must produce no observable effect "at the level in question." Accordingly, subsection (b) defines "exposure" for purposes of this exemption to mean the "reasonably anticipated rate of exposure for an individual to a given medium."

The reasonably anticipated rate of exposure will vary from case to case. It may be reasonably anticipated that food will be ingested once each day, or once each week, and so on. An individual may use a product containing a high level of a listed substance, but use the product only once a year. What rate of exposure is reasonably anticipated from a given medium, such as a certain type of food or a consumer product, will depend upon the medium, its anticipated use and other circumstances. For example, the publisher of a newspaper using inks containing a listed chemical may not reasonably anticipate that a reader will ingest the Sunday edition, but may reasonably anticipate other contact. A manufacturer of cardboard boxes may not reasonably anticipate the ingestion of a box, but may reasonably anticipate that the box will be used to package food products into which a chemical may migrate. A manufacturer of baby cribs might reasonably anticipate that an infant will chew or teethe on the railings.

Subsection (b) combines the definitions of "exposure" and "level in question" into a working formula. The level of exposure which must produce no observable effect assuming exposure at one thousand times the level in question is the product of the concentration of the chemical in the medium and the reasonably anticipated rate of exposure to individuals to that medium. Under this formula, a certain daily exposure to a chemical in a food product could be calculated by taking into account the concentration of the chemical in the food (in micrograms of chemical per gram of food), and multiplying that concentration times the quantity ingested (in grams of food per day). The product of this multiplication yields the quantity of chemical ingested in that food (in micrograms of chemical per day). This level must not exceed the level derived pursuant to this article.

The rate of exposure to a given medium of exposure is itself subject to fluctuation. Different individuals take in different amounts of air, water and food. Some may have considerably more exposure to a product than others. It is, therefore, also necessary to establish certain assumptions about particular media. This is accomplished in subsection (c). However, scientifically more appropriate or specific data may be used where available.

Paragraph (1) provides that, where appropriate, the assumptions set forth in section 12721, subsection (d) should apply. Paragraph (1)A. of that subsection assumes ingestion of two (2) liters of drinking water per day. Paragraph (1)B. assumes

inhalation of twenty (20) cubic meters of air per day. These values are drawn from the Report of the Task Group on Reference Man, published in 1975 by the International Commission on Radiological Protection, and are consistent with assumptions utilized in regulatory toxicology for these media.

Paragraph (d)(2) of section 12721 provides that different assumptions should be used where the exposure is expected to affect only a subpopulation to which different assumptions properly apply. Certain subpopulations need to be addressed where circumstances involve particular products or environmental conditions which may pose a possible exposure risk to a distinct group of people. For example, certain products may be used primarily by women. Paragraph (d)(2) provides different assumptions for various subpopulations for the ingestion of water and inhalation of air.

Paragraph (d)(3) of section 12721 provides a specific set of assumptions for exposures in the workplace, since workers are normally exposed for only a portion of the day, for a limited number of days each week, for a limited number of weeks per year. The net result of these assumptions, which are based upon well-accepted conventions, is that occupational exposures producing no observable effect within the meaning of the Act may involve slightly higher concentrations of the chemical.

It is anticipated that exposures will occur in the workplace to persons other than employees, such as customers, visitors or solicitors. These individuals will probably spend less time in that location as an employee. The Agency believes it is appropriate to differentiate between the potential exposure that may befall a temporary visitor and that of an employee. Therefore, paragraph (d)(3) of section 12721 assumes such persons will visit the premises one hour per month, and further assumes that they will inhale 1.25 cubic meters of workplace air during each visit.

Subsection (c)(1) does not apply to exposures to consumers, since that paragraph refers to the "average rate" of intake. As discussed above, the application of average rates of exposure to reproductive toxicants may not be appropriate.

Accordingly, subsection (c)(2) of this section provides assumptions for exposure resulting from the consumption of goods or consumer products as are described in section 12601, subsection (b). The reasonably anticipated rate of consumption by the product user, not the per capita consumption of the general population, is the standard. Data on the rate of intake should be based on the data available for general categories of products, such as the U.S. Department of Agriculture Home Economic Research Report on Foods Commonly Eaten by Individuals: Amount Per Day and Amount Per Eating Occasion, where available.

One commentator recommended that the regulation provide a means of dealing with variability and fluctuation of the "rate of exposure" term used to calculate the level of exposure, since some persons have a higher rate of exposure than others, though setting the anticipated rate at the highest rate may require a

warning to all users of a product on the basis of occasional high consumption. (C-20, p. 11.) The Agency has attempted to provide a means of dealing with these variables in consumer products. Exposure assessment need only be based upon the reasonably anticipated rate of exposure. To further clarify the Agency's intent, the March 29 proposal provided that it is the reasonably anticipated rate of exposure for "average" users which must be assessed. Therefore, it appears that this concern has been resolved.

One commentator recommended that the same rules should apply in determining exposure to consumer products for carcinogens as for reproductive toxicants, pointing out that under section 12721(d)(4), exposure to consumer products is calculated using the average rate of intake or exposure for users of the consumer product, and recommending that section 12821 should have exactly the same language. (Exh. 7, p. 63.) However, unlike chemicals known to the state to cause cancer, averaging the exposure or intake to yield a daily exposure over lifetime may not be appropriate for reproductive toxins. Since some reproductive effects, such as teratogenic responses or birth defects, may reflect an acute response during a brief period of intrauterine exposure, exposure to chemicals producing such effects should be assessed on the basis of short term exposure.

Therefore, when one evaluates such a reproductive toxin, one needs to view the exposure as the one that may cause the acute effect. For example, if a food is eaten once per week, and if that food contains a teratogen, a proper assessment would require the assumption that ingestion of that food will occur on any day and, hence, every day) of the pregnancy. In other words, averaging to a daily intake would be inappropriate, since the embryonic response ought to be assumed to occur on the day of the ingestion of that food.

If it is scientifically more appropriate to evaluate a reproductive toxicant for chronic toxicity, this section does permit it.

Under paragraph (c)(3), for long term exposures affecting the developing young, the level of exposure is to be based on the reasonably anticipated rate of exposure for the mother during the nine-month gestation period, since maternal intake would be the means by which the intrauterine exposure would occur. Thus, if the amount of the chemical from a source of exposure during the entire gestation period exceeds one one-thousandth of the level which produces no observable effect, the exemption does not apply, and a warning must be provided.

ADDENDUM TO
FINAL STATEMENT OF REASONS
22 CALIFORNIA CODE OF REGULATIONS DIVISION 2

Sections 12701, et seq. - No Significant Risk Levels
Sections 12801, et seq. - No Observable Effect Levels

At page 60 of the Final Statement of Reasons, the summary of the recommendation made by one commentator (C-24, p. 2) was incomplete due to clerical omission of part of the sentence. The first sentence of the third paragraph on that page should have read:

> "One commentator recommended that, as an alternative to deleting this section, the Agency should clarify that if the state or federal agency responsible for regulating that chemical has admitted inability to assess the level of risk, section 12713 does not apply, or alternatively exclude alcoholic beverages from 12713 (d)."

The Agency's response to this comment remains unchanged

One commentator testified at the July 29 hearing that overly conservative no significant risk levels would place a burden on small businesses. (T 33:10-34:24.) Under the Act, no person in the course of doing business, which includes any business with ten or more employees, shall knowingly and intentionally expose any individual to a chemical known to the state to cause cancer or reproductive toxicity without first giving clear and reasonable warning. Exposures which the business can show would pose no significant risk of cancer are exempt. The Act is self-executing in that its provisions may be enforced by certain public prosecutors and any person in the public interest, regardless whether the Agency adopts any specific no significant risk levels.

The regulations adopted by the Agency provide for "safe harbor" no significant risk levels. Businesses are not bound to use these levels, but may do so to avoid the burden of developing no significant risk levels of their own. Thus, it is the Act, not the regulations, which places the burden on small businesses of showing that their exposures pose no significant risk. Since the Agency's regulations provide non-binding "safe harbor" exposure levels, the Agency's regulations actually provide a relief to small businesses, not a burden. Even assuming that the Agency were to adopt overly conservative levels, the regulations would still provide a means to escape liability, not to impose it. (The Agency believes that the levels it has adopted are not overly conservative.) Accordingly, the Agency maintains that the regulations have no impact on small businesses.