FINAL
STATEMENT OF REASONS
22 CALIFORNIA CODE OF REGULATIONS

Section 12705(b) - Specific Regulatory Levels Posing No Significant Risk: Aldrin, Asbestos, Carbon tetrachloride, DDT/DDE/DDD, para-Dichlorobenzene, Dieldrin, 1,4-Dioxane, N-Nitrosodipropylamine, Urethane

The Safe Drinking Water and Toxic Enforcement Act of 1986 (hereinafter the Act) prohibits a person in the course of doing business from knowingly and intentionally exposing any individual to a chemical that has been listed as known to the State to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual (Health & Saf. Code Sec. 25249.6). The Act also prohibits a business from knowingly discharging a listed chemical into water or onto or into land where such chemical passes or probably will pass into a source of drinking water (Health & Saf. Code Sec. 25249.5).

For chemicals known to the state to cause cancer, an exemption is provided by the Act when a person in the course of doing business is able to demonstrate that an exposure for which it is responsible poses no significant risk, or that a discharge which otherwise complies with applicable requirements would result in an exposure through drinking water at a level which poses no significant risk (Health & Saf. Code Sec. 25249.10 and 25249.11).

A determination that a level of exposure poses no significant risk can be made utilizing regulations that have previously been adopted by the Health and Welfare Agency (Agency) (Sec. 12701 to 12721, Title 22, California Code of Regulations) (unless otherwise specified, all section references are to Title 22, CCR). Section 12701 describes alternative methods for making such a determination. One such method is through the application of the specific regulatory level established for the chemical in question in Section 12705. A level specified in Section 12705(b) supersedes Section 12709 (Exposure to Trace Elements), Section 12711 (Levels Based on State or Federal Standards), or Section 12713 (Exposure to Food, Drugs, Cosmetics and Medical Devices).

Procedural Background

On November 16, 1989, the Agency issued a notice of proposed rulemaking advising that the Agency intended to adopt a "no significant risk" level for aldrin, asbestos, carbon tetrachloride, DDT, DDE and DDD (in combination), para-dichlorobenzene, dieldrin, 1,4-dioxane, N-nitrosodipropylamine, and urethane. Pursuant to such notice, on January 18, 1990, a public hearing was held to receive public comments on the proposed regulation. Fifteen pieces of correspondence commenting on

Section 12705(b) were received. No comments were received at the public hearing.

On February 16, 1990, the Agency issued a Notice of Public Availability of Changes to Proposed Regulations Regarding the Safe Drinking Water and Toxic Enforcement Act of 1986. The notice afforded interested parties the opportunity to provide to the Agency their post-hearing comments on proposed modifications to proposed Section 12705 during a 15-day comment period. The comment period closed March 5, 1990. No post-hearing comments were received.

Purpose of Final Statement of Reasons

This final statement of reasons sets forth the reasons for the final regulation adopted by the Agency for Section 12705(b), and responds to the objections and recommendations submitted regarding the regulation. 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.

Some parties included in their written or oral comments remarks and observations about the regulation which do 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 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 Section 12705(b).

Necessity for Adoption of Regulations

For chemicals known to the State to cause cancer, the Act exempts discharges, releases and exposures which, making certain assumptions, pose no significant risk. 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 chemical. However, the Act does not further clarify when a chemical risk is not significant, nor specify levels of chemical exposure posing no significant risk. Existing regulations describe methods for calculating levels which pose no significant risk.

This regulation provides "safe harbor" no significant risk levels which will allow persons to determine whether a discharge, release or exposure is exempt from the provisions of the Act.

Section 12705(b)

This proposed regulation adopts the following no significant risk levels in Section 12705(b):

Aldrin	0.04 microgram per day
Asbestos	100 fibers inhaled/day*
	*Fibers equal to or greater than 5 micrometers in length and 0.3 micrometers in width, with a length to width ratio of greater than or equal to 3:1 as measured by phase contrast microscopy.
Carbon tetrachloride	5 micrograms per day
DDT, DDE and DDD (in combination)	2 micrograms per day
para-Dichlorobenzene	20 micrograms per day
Dieldrin	0.04 microgram per day
1,4-Dioxane	30 micrograms per day
N-Nitrosodipropylamine	0.1 microgram per day
Urethane	0.7 microgram per day

This proposed regulation simultaneously repeals the no significant risk level for these chemicals, where they exist, in Section 12711. Although

Section 12701 explicitly states that Section 12711 applies only when no specific level is established for the chemical in Section 12705, deletion of the chemical and its level from Section 12711 is necessary for clarity and to avoid confusion. The proposed levels represent the level of exposure to the chemical which is calculated to result in no more than one excess case of cancer in an exposed population of 100,000, assuming exposure over a 70-year lifetime (10^{-5} lifetime risk of cancer), and are based on the following risk assessment documents prepared, or reviewed by the California Department of Health Services (CDHS), Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, in accordance with the principles in Section 12703:

Integrated Risk Information System: Aldrin. CASRN 309-00-2. U.S. Environmental Protection Agency (EPA). EPA Environmental Criteria and Assessment Office, Cincinnati, OH. December 1, 1988.

"Public Hearing to Consider the Adoption of a Regulatory Amendment Identifying Asbestos as a Toxic Air Contaminant," February 10, 1986, "Part B - Health Effects of Asbestos," prepared by the Department of Health Services, January 1986.

"Proposition 65 Risk-Specific Intake Levels: Carbon Tetrachloride," dated July 1, 1988.

Integrated Risk Information System: p,p'-Dichlorodiphenyltrichloroethane (DDT). CASRN 50-29-3. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office, Cincinnati, OH. August 22, 1988.

Integrated Risk Information System: p,p'-Dichlorodiphenyldichloroethane (DDE). CASRN 72-55-9. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office, Cincinnati, OH. December 1, 1988.

Integrated Risk Information System: p,p'-Dichlorodiphenyl-dichloroethane (DDD). CASRN 72-54-8. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office, Cincinnati, OH. December 1, 1988.

"Proposed Maximum Contaminant Level: 1,4-Dichlorobenzene (p-Dichlorobenzene)," Hazard Evaluation Section, Department of Health Services. 1987.

Integrated Risk Information System: Dieldrin. CASRN 60-57-1. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office, Cincinnati, OH. July 1, 1989.

"Risk-Specific Intake Levels for the Proposition 65 Carcinogen 1,4-Dioxane," dated July, 1989.

Integrated Risk Information System: N-Nitrosodi-N-propylamine. CASRN 621-64-7. U.S. Environmental Protection Agency. Environmental Criteria and Assessment Office, Cincinnati, OH. January 1, 1988.

"Risk-Specific Intake Levels for the Proposition 65 Carcinogen Urethane," dated November, 1989.

Aldrin and Dieldrin

Cancer potency estimates for aldrin calculated from data on liver carcinomas in female and male C3H mice were 23 $(mg/kg\text{-}day)^{-1}$ and 18 $(mg/kg\text{-}day)^{-1}$, respectively. From a study of liver carcinomas in male B6C3F1 mice, a cancer potency of 12 $(mg/kg\text{-}day)^{-1}$ was calculated. Since all three slope factors were very similar, their geometric mean of 17 $(mg/kg\text{-}day)^{-1}$ was chosen for estimating risks from exposure to aldrin. From this value, the intake level associated with a 10^{-5} lifetime risk of cancer is 0.04 microgram per day.

For dieldrin, the geometric mean of 13 cancer potency estimates calculated from liver carcinoma data in both sexes of several strains of mice was calculated to be 16 $(mg/kg\text{-}day)^{-1}$. From this value, the intake level associated with a 10^{-5} lifetime risk of cancer is 0.04 microgram per day.

One commentor (C-11) argued that aldrin and dieldrin should not be listed as known to cause cancer: the mouse response to these chemicals appears to be unique to that species, and epidemiological data do not indicate an increased cancer risk of any type in workers with long-term exposures to high levels of these chemicals. The commentor also objected to the use of the linearized multistage model in the risk assessment, stating that this model is not appropriate, because it is not sensitive to the observed dose response behavior, and is unlikely to provide a realistic estimate of potency in humans, particularly after high to low dose and interspecies extrapolation. The commentor suggested that the panel's designation of the International Agency for Research on Cancer (IARC) be extended to include the World Health Organization (WHO), which IARC is a part of. Consequently, the Agency should consider WHO's acceptable daily intake for aldrin and dieldrin of 7 micrograms per day in setting the no significant risk level; human data suggests that levels of intake of aldrin and dieldrin exceeding 7 micrograms per day are without any adverse effect.

The commentor should note that the issue of "listing" a chemical as a carcinogen is not the subject of this regulation. Aldrin and dieldrin were listed in July 1, 1988 as a result of the Scientific Advisory Panel's recommendation.

The selection of the animal data and the use of the linearized multistage model in the risk assessments which were the basis for the proposed levels for aldrin and dieldrin are consistent with the guidelines in Section 12703. As with any person subject to the Act, the commentor always has the option of using an alternative no significant risk level based on his own risk assessment, utilizing data, principles and assumptions which he can establish as being scientifically valid. Pursuant to Section 12701, the no significant risk levels in Section 12705 are intended to provide safe harbors and do not preclude the use of alternative levels that can be demonstrated by their users to be scientifically valid.

The commentor also appears to confuse the listing of chemicals designated by IARC to be carcinogenic under the authoritative body provision with this proposed regulation. This designation of IARC is intended to apply to the listing of chemicals only, and only to IARC itself, not to the larger organization to which it belongs, or other programs within that organization. As was discussed in the previous paragraph, levels other than those adopted in Section 12705 may be used for purposes of determining compliance with the Act. The commentor may use the WHO acceptable daily intake, provided that he can show that exposure to aldrin or dieldrin at that level poses no significant risk of cancer, within the meaning of the Act.

Two commentors (C-14 and 15) recommended that the range of potency estimates for dieldrin should be given -- in addition to the results of taking a geometric mean --- in order to show the potential error range for underestimating potency. The summary of risk assessments in the Initial Statement of Reasons is intended to provide only brief discussions on how the proposed level was derived. The risk assessment documents used as the basis for the proposed regulatory levels are cited in the Initial Statement of Reasons to allow readers to refer to these documents for further information. The potency estimates for dieldrin are presented in the source document from the Integrated Risk Information System database as ranging from 7.1 to 55 $mg/kg/day^{-1}$.

Pursuant to Section 12705(c), which requires the lead agency to provide an opportunity for the Scientific Advisory Panel to review and comment on any proposed no significant risk level, the proposed levels for aldrin and dieldrin and the risk assessment documents which provide the basis for these levels were submitted to the Scientific Advisory Panel on October 29, 1989. No panelists presented specific recommendations on, or objections to, the proposed levels.

Asbestos

Linear models developed and/or used by earlier investigators were used to estimate risks of mesothelioma and lung cancer to the general population. The models extrapolate risks observed in numerous occupationally exposed

cohorts to lower levels of asbestos found in the general environment. Based on best estimates and approximate upper confidence limits for the group theoretically at highest risk for mesothelioma (female nonsmokers), it was calculated that exposure to asbestos at 0.0001 fiber per cm^3 (= 100 fibers per m^3) was associated with excess lifetime risk values of up to 20 per 100,000. A concentration of 100 fibers per m^3 multiplied by an inhalation rate of 20 m^3/day yields a daily exposure of 2,000 fibers corresponding to a cancer risk of up to 20 per 100,000. From these values, the Agency has proposed an exposure of 100 fibers inhaled per day measured by phase contrast microscopy as one associated with a 10^{-5} risk, for purposes of Section 12705(b). The fiber count can be converted to total fibers measurable by transmission electron microscopy by multiplying by 100 to 1,000.

Several comments dealing with the proposed level for asbestos were received (C-1, C-2, C-6, C-13, C-14, and C-15). Four of these comments (C-1, C-2, C-6, and C-13) recommended that the word "inhaled" be added to the proposed level. Since this recommendation is consistent with the Agency's intent to retain the same level for asbestos as is presently in effect in Section 12711, the final version incorporates this change.

Two commentors (C-14 and 15) stated that the explanation given for the proposed level for asbestos is "inconsistent with the cited data and is consistent with a level 20 times lower." They point out that a range of risks was presented and the lowest risk selected with no justification offered. The commentors correctly indicate a need for greater clarity in the statement of reasons, which originally pointed out the range of risk estimates taken from the CDHS risk assessment document on asbestos prepared for the Air Resources Board's toxic air contaminant program. In that document, the calculated risks for inhalation exposure to 100 fibers/m^3 ranged from 1 to 11 cases per 100,000 for lung cancer in male smokers, and from 4 to 20 cases per 100,000 for mesothelioma in female nonsmokers.

The no significant risk level for asbestos is based on the most restrictive estimated cancer risk (20 excess mesothelioma cases per 100,000 in female nonsmokers) for daily lifetime exposures to 100 fibers/m^3. This airborne asbestos concentration level corresponds to a level of intake of 2,000 fibers/day (100 fibers/m^3 x 20 m^3/day). For a 10^{-5} cancer risk, the daily intake is calculated to be 100 fibers inhaled per day.

Pursuant to Section 12705(c), which requires the lead agency to provide an opportunity for the Scientific Advisory Panel to review and comment on any proposed no significant risk level, the proposed level for asbestos and the risk assessment document which provides the basis for this level were submitted to the Scientific Advisory Panel on September 16, 1988. The September 16, 1988 meeting was the first opportunity for the panel

members to review risk assessments for a number of listed chemicals, and resulted in many general comments on the risk assessment procedure.

Several panelists emphasized the risk of one excess case of cancer per 100,000 people per lifetime by this risk assessment ought to be remembered as an outer or upper bound (or a "plausible upper bound"), and that the actual risk is most likely lower. This is consistent with the approach generally used in quantitative risk assessment, with the level established indicating a value that generally would not underestimate the risk. One panelist pointed out that a number of models exist for quantitative risk assessment and recommended presentation of several models with a rationale given for the choice of one model over another. The recommendations already were included in risk assessment documents which were prepared by staff of the Department of Health Services for the same chemicals (but under other regulatory programs, e.g., establishing drinking water standards or assessing toxic air contaminants), and which provided the basis for the documents prepared for the September 16 discussion and proposed level.

During the panel's discussion of the risk assessment for asbestos, several panel members recommended that only inhaled asbestos be regulated under the Act, as current scientific evidence indicates that there is no significant risk of cancer from ingested asbestos. Following the panel's recommendation, the Agency listed asbestos as a chemical that poses no significant risk by ingestion under Section 12707. No panelists presented specific recommendations on, or objections to, the proposed level.

Carbon tetrachloride

Using data from a study of mice receiving carbon tetrachloride orally, a carcinogenic potency factor of 0.2 $(mg/kg\text{-}day)^{-1}$ was estimated. At this potency estimate, the air concentration associated with a 10^{-5} risk of cancer is 250 ng/m^3, and the intake level is 5 micrograms per day.

No recommendations on, or objections to, the proposed level were received during the public comment period.

Pursuant to Section 12705(c), which requires the lead agency to provide an opportunity for the Scientific Advisory Panel to review and comment on any proposed no significant risk level, the proposed level for carbon tetrachloride and the risk assessment document which provides the basis for this level were submitted to the Scientific Advisory Panel on September 16, 1988. General comments offered by the panel on the risk assessments have been discussed in the section on asbestos.

With regard to carbon tetrachloride, one panel member stated that the risk assessment document should include a discussion of the differences in pharmacokinetics and mechanisms of action between humans and

laboratory animals. Another panel member stressed the importance of referring to the no significant risk level as the level corresponding to a plausible upper bound risk of 10^{-5} because, in a chemical such as carbon tetrachloride, this would allow CDHS to recommend a level and identify the factors which could affect the cancer potency estimate, rather than calculating different estimates based on different models. As discussed above, these discussion points were addressed in previous CDHS documents referenced in the risk assessment document; they had no impact on the proposed level. No panelists presented specific recommendations on, or objections to, the proposed level.

DDT, DDE and DDD

(1) DDT

Data from oral studies using various strains of mice and rats yielded cancer potency estimates ranging from 0.082 $(mg/kg\text{-}day)^{-1}$ to 1.04 $(mg/kg\text{-}day)^{-1}$. In order to avoid excluding relevant data, a geometric mean of the estimates was used for the overall cancer potency of 0.34 $(mg/kg\text{-}day)^{-1}$. From this value, the intake level associated with a 10^{-5} lifetime risk of cancer is 2 micrograms per day.

(2) DDE

A cancer potency estimate of 0.34 $(mg/kg\text{-}day)^{-1}$ was calculated as the geometric mean of six cancer potency estimates derived from incidence data by sex from two studies using mice, and one using hamsters. From this value, the intake level associated with a 10^{-5} lifetime risk of cancer is 2 micrograms per day.

(3) DDD

Data on liver tumors in male CF-1 mice from an oral study was used to calculate a cancer potency of 0.24 $(mg/kg\text{-}day)^{-1}$. From this value, the intake level associated with a 10^{-5} lifetime risk of cancer is 3 micrograms per day.

Because DDT, DDE and DDD have a common site of carcinogenic action in animal bioassays, have similar cancer potencies, and can be interconverted in the environment or in the body (DDE and DDD are metabolites of DDT), the cancer risk exceeds 10^{-5} when the combined daily intake of the three compounds exceeds 2 micrograms.

No recommendations on, or objections to, the proposed level were received during the public comment period.

Pursuant to Section 12705(c), which requires the lead agency to provide an opportunity for the Scientific Advisory Panel to review and comment on

any proposed no significant risk level, the proposed level and the risk assessment documents which provide the basis for the level were submitted to the Scientific Advisory Panel on October 29, 1989. No panelists presented specific recommendations on, or objections to, the proposed level.

para-Dichlorobenzene

Both standard and time-dependent forms of the multistage polynomial were fit to dose-response data for hepatocellular carcinomas and adenomas in the male B6C3F1 mouse, the most sensitive site, sex and species tested. The time-dependent analysis resulted in a potency estimate for male mice of 0.003 $(mg/kg\text{-}day)^{-1}$; the standard analysis, of 0.002 $(mg/kg\text{-}day)^{-1}$. Human potency estimates of 0.04 and 0.03 $(mg/kg\text{-}day)^{-1}$ for the time-dependent and standard analyses, respectively, are obtained by applying the standard interspecies extrapolation procedures specified in Section 12703. Using the potency derived from the time-dependent analysis, 0.04 $(mg/kg\text{-}day)^{-1}$, the intake level associated with a 10^{-5} lifetime risk of cancer is 20 micrograms per day.

One commentor (C-12) contended that the no significant risk level for para-dichlorobenzene should be 750 micrograms per day, based on an EPA risk assessment. The commentor further states that para-dichlorobenzene was incorrectly represented to the panel at the time it was considered for listing as an EPA Group B2 carcinogen (probable human carcinogen), and that the chemical was listed based on data from studies in rats and mice, which are of questionable significance. According to the commentor, in selecting data on liver tumors in male B6C3F1 mice as the basis for calculating a cancer potency estimate, CDHS failed to consider all relevant evidence.

The listing of para-dichlorobenzene as a chemical known to the State to cause cancer is not the issue of the proposed regulation. However, the commentor must note that the classification of a chemical as a Group C carcinogen (possible human carcinogen) by EPA does not preclude its listing as a carcinogen under the Act, if there is sufficient evidence of its carcinogenicity.

The risk assessment for para-dichlorobenzene was based on data from the most sensitive site, sex and species, which is required under Section 12703 in the absence of scientifically more appropriate data. CDHS considered the data on para-dichlorobenzene not to be sufficient to warrant deviating from the default methodology. The commentor recommended a no significant risk level of 750 micrograms per day based on an EPA risk assessment. The risk assessment referred to by this commentor is EPA's calculation of the maximum contaminant level goal (MCLG) for para-dichlorobenzene, and is based on the subchronic toxicity of the chemical, rather than its carcinogenicity. As such, this assessment is not appropriate for use as the basis for establishing a

level which poses no significant risk of cancer. The commmentor appears to have confused an EPA risk management decision with a risk assessment. In the same document provided by the commentor, EPA's cancer risk coefficient for para-dichlorobenzene is 0.02 $(mg/kg\text{-}day)^{-1}$, which leads to a 10^{-5} risk of 35 micrograms/day, a value not too dissimilar from the proposed level. The commentor makes no mention of this cancer risk assessment.

Two commentors (C-3 and C-4) stated that use of data on liver tumors in B6C3F1 mice in the risk assessment overestimates human cancer risk for para-dichlorobenzene due to evidence indicating that there is a high incidence of spontaneous liver tumors in this strain and the identification of a cellular oncogene in these tumors. These commentors suggested that the same approach which was used in calculating the proposed no significant risk level for aldrin -- i.e., using the geometric mean of the slopes from strains and sexes other than male B6C3F1 mice -- be used for calculating the level for para-dichlorobenzene.

The use of data for liver tumors in male mice is consistent with the default assumptions in Section 12703, which requires using the most sensitive site, sex and species, unless an alternative approach is more appropriate. For aldrin, the geometric mean of the cancer potency estimates was used because the slope factors obtained from the data in female C3H, male C3H and male B6C3F1 mice were very similar; hence, the concordance of these studies provided the basis for the more appropriate approach for aldrin.

Pursuant to Section 12705(c), which requires the lead agency to provide an opportunity for the Scientific Advisory Panel to review and comment on any proposed no significant risk level, the proposed level for para-dichlorobenzene and the risk assessment document which provides the basis for this level were submitted to the Scientific Advisory Panel on October 29, 1989. No panelists presented specific recommendations on, or objections to, the proposed levels.

<u>1,4-Dioxane</u>

Based on the combined incidence of hepatocellular adenomas and carcinomas in female B6C3F1 mice, a cancer potency of 0.027 $(mg/kg\text{-}day)^{-1}$ was selected. The intake level associated with a 10^{-5} risk of cancer is 30 micrograms per day for regulatory purposes.

Commentors C-3 and C-4 offered the same arguments against reliance on liver tumors in B6C3F1 mice in calculating the cancer potency for 1,4-dioxane as they did for para-dichlorobenzene. Again, the no significant risk level is based on data representing the most sensitive site, sex and species (hepatocellular adenomas and carcinomas in female B6C3F1 mice), as required by Section 12703.

Three commentors (C-5, C-8, and C-10) contend that the proposed no significant risk level for 1,4-dioxane is unjustifiably low, and that the risk assessment should take into consideration important data on pharmacokinetics and mechanisms of action, rather than using the default assumptions. Two of these commentors (C-8 and C-10) recommend a no significant risk level of 56 milligrams per day based on a risk assessment using a physiologically-based pharmacokinetic model. Commentor C-10 asserts that in proposing to adopt a no significant risk level of 30 micrograms per day for 1,4-dioxane, the Agency has been unable to make a showing of the necessity to establish a no significant risk level "over 1000 times lower than the best available science indicates is needed to protect public health fully."

CDHS did review the pharmacokinetic data on 1,4-dioxane and concluded that the data were not adequate for use in a risk assessment for two main reasons: (a) there are inadequate data in mice (the most sensitive species) for making pharmacokinetic calculations, i.e., for determining the relationship between the applied dose of 1,4-dioxane and the concentration of the chemical or its metabolites in target tissues; and (b) it is not known whether the active carcinogen is 1,4-dioxane or its metabolites (e.g., betahydroxyethoxyacetic acid), and the results of a pharmacokinetic-based risk assessment would depend strongly on which agent is assumed to be the active carcinogen in target tissues.

Commentor C-8 states that, "using highly conservative assumptions," the EPA has calculated a no significant risk level of 60 micrograms per day. Additionally, the commentor contends that the scientific evidence indicates the existence of a threshold, and when a threshold is assumed, the no significant risk level is calculated to be 700 micrograms per day.

The CDHS risk assessment on 1,4-dioxane was performed using the principles and assumptions in Section 12703, with respect to data selection and use of a no threshold model. EPA's risk assessment was based on data on squamous cell carcinomas of the nasal turbinates in male Osborne-Mendel rats from an oral study. Besides not being the most sensitive study, there is some question that the nasal turbinate carcinomas observed in this study may be due to the route of administration rather than being a systemic response, particularly because nasal turbinate tumors were not found in a rat inhalation study.

Finally, as with any person subject to the Act, the commentors always have the option of using an alternative no significant risk level based on their own risk assessment, utilizing data, principles and assumptions which they can establish as being scientifically valid. Pursuant to Section 12701, the no significant risk levels in Section 12705 are intended to provide safe harbors and do not preclude the use of alternative levels that can be demonstrated by their users to be scientifically valid.

Pursuant to Section 12705(c), which requires the lead agency to provide an opportunity for the Scientific Advisory Panel to review and comment on any proposed no significant risk level, the proposed level for 1,4-dioxane and the risk assessment document which provides the basis for this level were submitted to the Scientific Advisory Panel on October 29, 1989. No panelists presented specific recommendations on, or objections to, the proposed level.

N-Nitrosodipropylamine

A human cancer potency value of 7 $(mg/kg\text{-}day)^{-1}$ is estimated from data on hepatocellular carcinomas in BD rats given N-nitrosodipropylamine (NDPA) in drinking water. From this value, the intake level associated with a 10^{-5} lifetime risk of cancer is 0.1 microgram per day.

Two commentors (C-14 and C-15) point out that the proposed no significant risk level for N-nitrosodipropylamine is derived from the EPA's Integrated Risk Information System (IRIS), and that the risk assessment guidelines used by EPA are not identical to those used by CDHS in deriving no significant risk levels under Proposition 65. They state that no mention is made in IRIS about whether the data from BD rats, which was selected as the basis for calculating the cancer potency estimate, represented the most sensitive site, species, and study. Existing risk assessments do undergo review by CDHS before they are used as the basis for any proposed no significant risk level. Although CDHS and EPA guidelines for conducting risk assessments are not identical, EPA risk assessments are reviewed to ensure that the selection of the study or studies, the assumptions, and the models are consistent with the risk assessment guidelines in Section 12703.

A 1967 study by Druckrey et al. (H. Druckrey, R. Pruessman, S. Ivankovic, and D. Schmahl, 1967, Organotropic carcinogenic effect of 65 different N-nitroso compounds on BD rats. Z. Krebsforsch. 69:103-201) in which N-nitrosodipropylamine (NDPA) was administered daily to BD rats is used as the basis for the EPA cancer potency estimate. CDHS has determined that this is the appropriate study to use, pursuant to Section 12703. Druckrey et al. do not provide summary statistics on tumors, but from their report, it may be inferred that the incidence of liver tumors in rats given 4, 8, 15 and 30 mg/kg-day of NDPA in drinking water were 14/16, 15/16, 15/15, and 1/1, respectively. The background incidence of liver tumors in BD rats is very low.

Because the tumor incidence in treated animals approaches 100% for all treatment groups, a time-dependent analysis is preferred to the standard multistage analysis, which gives a potency value of 3.8 $(mg/kg\text{-}day)^{-1}$ (corresponding to an estimate for potency in animals of 0.65 $(mg/kg\text{-}day)^{-1}$, and an interspecies scaling factor of 5.85). The following discussion shows how the analysis Druckrey provides is

equivalent to that performed by fitting the Weibull multistage model to the time-dependent tumor statistics of Druckrey. The Weibull analysis provides better estimates of potency than the standard analysis for this case where high tumor incidences are seen.

The Weibull model, fit to data on the time of death and tumor status of individual animals, relates the probability of tumor by time (t) to dose:

$$\text{Probability of tumor } (t,d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2)(t/T)^k] \quad \text{(Eqn. 1)}$$

for an animal with nominal lifespan T. "Cancer potency" in humans is given by the upper 95% confidence bound on q_1 with t set to the nominal lifespan T.

Druckrey et al. did not explicitly fit the Weibull model to tumor data, but instead derived empirical relationships of the form

$$dt_{50}^n = k$$

where d is the daily dose, k is an empirical constant, and t_{50} is the time for tumor induction in 50% of the animals treated a dose d.

For NDPA, Druckrey et al. reported that for animals treated at 4 and 30 mg/kg-day, the 50% induction time t_{50} was 300 days and 120 days, respectively. The term "n" is found to be 2.2. Thus, "k" for NDPA is 1.3×10^6 [$= 4 \times 300^{2.2} = 30 \times 120^{2.2} = d \times t_{50}^n$], when probability of tumor (in Eqn. 1, above) is 0.5. Since "k" is the same for the lowest and highest treatment groups, the dose response data indicate a linear dose response relationship so q_2 in Eqn. 1 is zero. Because background incidence of liver tumors in BD rats in negligible, q_0 in Eqn. 1 is also negligible. Thus, for the Druckrey et al. data, we have:

$$0.5 = 1 - \exp\,[-(q_1 d)(t_{50}/T)^{2.2}]$$

or

$$0.5 = 1 - \exp\,[-(q_1)(k)(T)^{-2.2}]$$

which can be rewritten

$$-\ln\,(1 - 0.5) = -\ln(1/2) = \ln(2) = q_1 k T^{-2.2}$$

That is, potency in animals, q_1, is given by

$$q_1 = [\ln(2)/k]\ .\ T^{2.2}$$

In this case, we should express the nominal lifespan for rats in days in order for the units of the analysis to be consistent. EPA and CDHS typically assume a value of 2 years (730 days) for T. Thus, in animals

$$q_1 = [\ln(2)/1.3 \times 10^6][730]^{2.2}$$
$$= 1.22 \text{ (mg/kg-day)}^{-1}$$

To obtain the human potency, q_1 is multiplied by the interspecies scaling factor [Z = (Body weight humans/Body weight animals)$^{1/3}$].

$$q_{human} = q_1 \times Z$$
$$= 1.22 \cdot (70/0.35)^{1/3}$$
$$= 7.14 \text{ (mg/kg-day)}^{-1}$$

which is within 2% of the value EPA calculated from the statistics. There is one minor difference between this value and that given by EPA -- EPA used n = 2.3, a general value for nitrosamines. Here n = 2.2 was assumed, the value provided by Druckrey for NDPA.

These calculations do not provide an upper 95% confidence level on potency for this study. Since Druckrey et al. do not indicate statistical errors in their parameter estimates, it is not possible to derive an upper bound estimate.

Pursuant to Section 12705(c), which requires the lead agency to provide an opportunity for the Scientific Advisory Panel to review and comment on any proposed no significant risk level, the proposed level for NDPA and the risk assessment document which provides the basis for this level were submitted to the Scientific Advisory Panel on October 29, 1989. No panelists presented specific recommendations on, or objections to, the proposed level.

Urethane

Cancer potency values were calculated from 38 oral studies in rats, mice and hamsters. Mortality and pharmacokinetic effects were taken into account in the calculations where appropriate and where the necessary data were available. Alternative averaging procedures were used to indicate the range of probable values for the cancer potency of urethane.

The value of 1 (mg/kg-day)$^{-1}$, which is the mean of the human cancer potency estimates derived from data on mouse lung tumors, was selected as the potency estimate for urethane. The intake level associated with a 10^{-5} risk of cancer is 0.7 microgram per day.

Two comments were received on the proposed level for urethane. One commentor (C-9) recommended that the proposed level of 0.7 microgram per day be rejected as it was calculated using inadequate studies, and suggested that no level be established at this time. The commentor contends that adopting a level "which has been severely criticized by the Scientific Advisory Panel and by prominent experts in the field...would clearly be arbitrary and capricious and would violate section 12705(c)."

The Agency disagrees with this commentor's recommendation to reject the proposed level because it was based on inadequate studies. The risk assessment document for urethane states:

> "Ideally, cancer potency should be estimated from reasonably large experiments (at least 50 animals per group), with continuous exposure at a constant dose rate (in mg/surface area) throughout the lifetime of the animals, and with the use of more than one dose level and adequate controls. The incidence of tumor types should be reported on a site specific basis, and when substantial early mortality in treated groups occurs data on tumors observed and time of death for individual animals is preferable."

Most of the many urethane studies do not meet the ideal criteria, and some are significantly deficient. However, CDHS concluded that, in addition to one multiple dose study, "several other oral studies are considered suitable for potency analysis in spite of the study design being less than ideal: where a single dose level is employed, this is not a serious disadvantage if several studies are available for comparison, as is the case for urethane."

Based on its analysis of the overall distribution of cancer potency estimates from each oral study, CDHS determined that, as a body of data, the results are consistent with one another. Further, CDHS concluded that by considering a large number of studies together, the statistical power obtained is equivalent to -- or, in the case of urethane, is greater than -- the power of a single multiple dose study of good quality.

Among the studies identified by CDHS was one which employed continuous dosing at multiple dose levels in concurrently exposed groups. However, the published data from this study reported total benign and total malignant tumors, and did not identify the types of tumors in the experimental and control groups, nor report tumor incidence data by sex. The original laboratory data from this study was obtained, re-analyzed and used by CDHS in calculating cancer potency estimates. Although this approach was criticized by one panelist, the Agency has determined such an approach to be reasonable. Since the primary goal of the risk assessment process is to enable a description of the dose-response relationship of a given chemical, the Agency believes that additional calculations based upon data that provided the basis for published papers (which often contain only summary tables) is appropriate. Since the origin of those data is referenced, and accessible to interested parties, those data may be evaluated by anyone who chooses to do so.

As with any person subject to the Act, the commentor always has the option of using an alternative no significant risk level based on his own risk assessment utilizing data, principles and assumptions which he can

establish as being scientifically valid. Pursuant to Section 12701, the no significant risk levels in Section 12705 are intended to provide safe harbors and do not preclude the use of alternative levels that can be demonstrated by their users to be scientifically valid.

Finally, the commentor does not appear to understand subsection 12705(c), which is not part of this proposed regulation. Establishing in regulation a safe harbor no significant risk level for urethane would not "violate" the regulation. Only proposing a numeric value in 12705(b) without allowing the Scientific Advisory Panel an opportunity for review and comment would be violative. The panel did have such an opportunity for review and comment, as noted below, and as noted by the commentor himself.

Another commentor (C-7) stated that the no significant risk level should be more restrictive and recommended 0.2 microgram per day, a level derived from a Weibull multistage time-dependent analysis using the study by Schmahl et al. The commentor criticized the proposed level because it was based on an average of different potency estimates which may include those derived from studies of questionable quality and of varying degrees of sensitivity. Although CDHS acknowledges that the Schmahl et al. study is reliable, in that it is the only study which employed continuous dosing at multiple dose levels in concurrently exposed groups, CDHS nevertheless chose not to use the cancer potency calculated from this study as the sole basis for the no significant risk level. For chemicals with a large number of nonstandard data sets, there is the possibility for extremely high or extremely low values. Because of the large number and the distribution of the values that can be estimated for urethane, CDHS found it more appropriate to use a measure of central tendency, instead of taking the greatest cancer potency value that can be calculated.

Pursuant to Section 12705(c), which requires the lead agency to provide an opportunity for the Scientific Advisory Panel to review and comment on any proposed no significant risk level, the proposed level for urethane and the risk assessment document which provides the basis for this level were submitted to the Scientific Advisory Panel on October 29, 1989.

One panel member questioned the acceptability of CDHS' rationale in taking together a group of studies -- which, individually, are not considered to be of sufficient quality -- and its use of raw, unpublished, non-peer reviewed laboratory data, in conducting the risk assessment for urethane. These concerns have been addressed above, in response to public comments submitted. Beyond these points, no panelists presented specific recommendations on, or objections to, the proposed level.

ADDENDUM
FINAL
STATEMENT OF REASONS
22 CALIFORNIA CODE OF REGULATIONS

Section 12705(b) - Specific Regulatory Levels Posing No Significant Risk: Aldrin, Asbestos, Carbon tetrachloride, DDT/DDE/DDD, para-Dichlorobenzene, Dieldrin, 1,4-Dioxane, N-Nitrosodipropylamine, Urethane

On page 7, paragraphs 2 and 3 are amended to read:

Two commentors (C-14 and 15) stated that the explanation given for the proposed level for asbestos is "inconsistent with the cited data and is consistent with a level 20 times lower." They point out that a range of risks was presented and the lowest risk was selected with no justification offered. ~~The commentors correctly indicate a need for greater clarity in the statement of reasons, which originally pointed out the range of risk estimates taken from the CDHS risk assessment document asbestos prepared for the Air Resources Board's toxic air contaminant program. In that document, the calculated risks for inhalation exposure to 100 fibers/m3 ranged from 1 to 11 cases per 100,000 for lung cancer in male smokers, and from 4 to 20 cases per 100,000 for mesothelioma in female nonsmokers.~~ The commentors' observations are correct because the summary of the asbestos risk assessment contained in the initial statement of reasons was incomplete. The level indicated as 100 fibers per m^3 should instead have read 100 fibers per day. The risk assessment used an airborne asbestos concentration level of 100 fibers per m^3, and extrapolated the cancer risks associated with this level using occupational data. The no significant risk level of 100 fibers inhaled per day was mathematically calculated using these cancer risk estimates.

In the CDHS risk assessment document, the calculated risks for inhalation exposure to 100 fibers/m^3 ranged from 1 to 11 cases per 100,000 for lung cancer in male smokers, and from 4 to 20 cases per 100,000 for mesothelioma in female nonsmokers. Contrary to the commentor's assumption that the lowest risk was selected, ~~The~~ the no significant risk level for asbestos is based on the most restrictive (i.e., highest) estimated cancer risk (20 excess mesothelioma cases per 100,000 in female nonsmokers) for daily lifetime exposures to 100 fibers/m^3. Selection of data from the most sensitive population is consistent with the risk assessment guidelines in Section 12703. This airborne asbestos concentration level corresponds to a level of intake of 2,000 fibers/day (100 fibers/m^3 x 20 m^3/day). For a 10^{-5} cancer risk, the daily intake is calculated to be 100 fibers inhaled per day.