IAPMO Internal Procedure

Conformity Assessment Document for

California Proposition 65 Compliance – Products or Materials.

Contents

Introduction

California Proposition 65, officially known as the Safe Drinking Water and Toxic Enforcement Act of 1986, was enacted as a ballot initiative in November 1986. The proposition protects the state's drinking water sources from being contaminated with chemicals known to cause cancer, birth defects or other reproductive harm, and requires businesses to inform individuals in California about exposures to such chemicals before the exposure occurs. Proposition 65 only applies to businesses with 10 or more employees. Proposition 65 requires the state to maintain and update a list of chemicals known to the state to cause cancer or reproductive toxicity.

These chemicals can be in the products that individuals purchase, in their homes or workplaces, or may be ones that are released into the environment in California. By requiring that this information be provided, Proposition 65 enables individuals to make more informed decisions about their exposures to these chemicals.

To guide businesses in determining whether a warning is necessary, the Office of Environmental Health Hazard Assessment (OEHHA) has developed safe harbor levels for many Proposition 65 listed chemicals. A safe harbor level identifies a level of exposure to a listed chemical that does not require a Proposition 65 warning. A business does not need to provide a warning if exposure in units of microgram per day (µg/day) to a chemical occurs at or below these levels. These safe harbor levels consist of No Significant Risk Levels (NSRLs) for chemicals listed as causing cancer and Maximum Allowable Dose Levels (MADLs) for chemicals listed as causing birth defects or other reproductive harm.

If OEHHA has not established a safe harbor level for a chemical, businesses that expose individuals to that chemical would be required to provide a Proposition 65 warning, unless the business can show that the anticipated exposure level will not pose a significant risk of cancer or reproductive harm[1]. OEHHA has adopted regulations that provide guidance for businesses in calculating their own safe level of exposure in the absence of an OEHHA safe harbor level. Regulations are available at Article 7 and Article 8 of Title 27, California Code of Regulations.

Determining anticipated levels of exposure to listed chemicals can be very complex. Although a business has the burden of determining if a warning is required, a business is discouraged from providing a warning that is not necessary (*i.e.,* over-warning for hazards).

The purpose of this Document is to determine if a specific product requires warnings in accordance with Proposition 65 regulations. The Document outlines methods for determining if humans may be exposed to chemicals associated with products/materials and if the levels of exposure are high enough such that a Proposition 65 warning for the product is required by law. If it is determined that a specific product may expose an individual to a chemical(s) on the Proposition 65 list at a significant level, this Document provides instructions for providing a warning for the product in accordance with the most up-to-date Proposition 65 regulations, including what chemical(s) is of concern and what health effect(s) is of concern.

[1] Under Proposition 65, toxicity of chemicals that affect either the ability of a human to reproduce or that causes direct toxicity to a fetus during development (birth defects) are grouped together in a warning, even though reproductive toxicity and developmental toxicity are two very different types of toxic effects, with some chemicals only affecting reproduction and others only linked with toxicity to a developing fetus.

IAPMO Conformity Assessment Document -2023 **California Proposition 65 Compliance – Products or Materials.**

1 General

1.1 Purpose

The purpose of this document is to establish methods to address the compliance of consumer products or materials with California Proposition 65 requirements. Product compliance is determined in accordance with this document and input from a product manufacturer and supplier.

1.2 Scope

This document is intended to cover specific consumer materials or products that include:

- Drinking Water Treatment Products
- Plumbing Products
- Pool and Spa Equipment
- Drinking Water Treatment Chemicals

The California Code of Regulations defines “consumer product” in § 25600.1. Definitions. as “any article, or component part thereof, including food, that is produced, distributed, or sold for the personal use, consumption or enjoyment of a consumer.” This Document addresses any potential exposures which may occur during the initial installation of a consumer product, whether the installation is by a professional or a consumer. This Document specifies some acceptable laboratory testing methods for various products/materials and exposure pathways. In addition, this document specifies methods which may be used to derive safe harbor levels, (No Significant Risk Levels (NSRLs) for cancer-causing chemicals and Maximum Allowable Dose Levels (MADLs) for chemicals causing reproductive toxicity), for chemicals specified on the Proposition 65 list for which no safe harbor levels have been derived. The Document is intended to be used by risk assessors and only applies to businesses with 10 or more employees.

1.3 Terminology

In this Document,

(a) "shall" is used to express a requirement, i.e., a provision that the user is obliged to satisfy to comply with the document;
(b) "should" is used to express a recommendation, but not a requirement;
(c) "may" is used to express an option or something permissible within the scope of the Document; and
(d) "can" is used to express a possibility or a capability.

Notes accompanying sections of the document do not specify requirements or alternative requirements; their purpose is to separate explanatory or informative material from the text. Notes to tables and figures are considered part of the table or figure and can be written as requirements.

1.4 Units of Measurement

SI units are the primary units of record in global commerce. In this document, the inch/pound units are shown in parentheses. The values stated in each measurement system are equivalent in application, but each unit system is to be used independently. All references to gallons are to U.S. gallons.

1.5 Limitations

The methodology outlined in this document is only applicable to California Proposition 65 requirements. Ultimately, the manufacturer and/or supplier is responsible for determining if a warning label should be used for a specific product. This Document also does not include continuous compliance management, sometimes seen in other documents or industry guidance documents. Use of this document is not a substitute for legal guidance regarding California Proposition 65 warning label requirements.

1.6 Significant Figures and Rounding

To determine conformance with the specifications in this document, the Absolute Method in ASTM E29 Document Practice for Using Significant Digits in Test Data to Determine Conformance with Specifications shall be used. The rounding procedure in Section 6.4 of ASTM E29 shall be used when rounding numbers.

2 Reference Publications

This document refers to the following publications and, where such reference is made, it shall be to the current edition of those publications, including all amendments published thereto.

ASTM International

ASTM E29
Standard Practice for Using Significant Digits in Test Data to Determine Conformance with Specifications

ISO
ISO 10993-1
Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process

NSF International
NSF/ANSI 42
Drinking Water Treatment Units - Aesthetic Effects

NSF/ANSI 44
Residential Cation Exchange Water Softeners

NSF/ANSI 53
Drinking Water Treatment Units - Health Effects

NSF/ANSI 55
Ultraviolet Microbiological Water Treatment Systems

NSF/ANSI 58
Reverse Osmosis Drinking Water Treatment Systems

NSF/ANSI/CAN 61
Drinking Water System Components - Health Effects

NSF/ANSI 62
Drinking Water Distillation Systems

NSF/ANSI 401
Drinking Water Treatment Units - Emerging Compounds/Incidental Contaminants

NSF/ANSI/CAN (NSF) 600
Health Effects Evaluation and Criteria for Chemicals in Drinking Water

U.S. EPA (U.S. Environmental Protection Agency)
U.S. Environmental Protection Agency (U.S. EPA). 1991. Guidelines for Developmental Toxicity Risk Assessment. EPA/600/FR-91/001. United States Environmental Protection Agency, Washington, DC, USA. Available at: https://www.epa.gov/sites/default/files/2014-11/documents/dev_tox.pdf.

U.S. Environmental Protection Agency (U.S. EPA). 1996. Guidelines for Reproductive Toxicity Risk Assessment. EPA/630/R-96/009. United States Environmental Protection Agency, Washington, DC, USA. Available at: https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf.

U.S. Environmental Protection Agency (U.S. EPA). 1998 - 2003. Series 870 – Health Effects Test Guidelines. United States Environmental Protection Agency, Washington, DC, USA. Available at: https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-870-health-effects-test-guidelines.

U.S. Environmental Protection Agency (U.S. EPA). 2001. Draft Protocol for Measuring Children's Non-Occupational Exposure to Pesticides by all Relevant Pathways. (EPA/600/R-03/026). Research Triangle Park, NC: National Exposure Research Laboratory, Office of Research and Development, U.S. EPA. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=10004SF1.TXT.

U.S. Environmental Protection Agency (U.S. EPA). 2005. Guidelines for Carcinogen Risk Assessment.
Risk Assessment Forum. EPA/630/P-03/001B. United States Environmental Protection Agency, Washington, DC, USA. Available at: https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

U.S. Environmental Protection Agency (U.S. EPA). (2011). Exposure Factors Handbook: 2011 Edition. National Center for Environmental Assessment, Washington, DC. EPA/600/R-09/052F, September 2011. Available at: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

U.S. Environmental Protection Agency (U.S. EPA). 2019a. Exposure Factors Handbook, Chapter 3: Ingestion of Water and Other Select Liquids. National Center for Environmental Assessment, Washington, DC. <http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=538153>

U.S. Environmental Protection Agency (U.S. EPA). 2019b. Guidelines for Human Exposure Assessment. (EPA/100/B-19/001). Washington, D.C.: Risk Assessment Forum, U.S. EPA. Available at: https://www.epa.gov/sites/default/files/2020-01/documents/guidelines_for_human_exposure_assessment_final2019.pdf.

U.S. Environmental Protection Agency (U.S. EPA). 2022. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United States Environmental Protection Agency, Washington, DC, USA. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

U.S. Environmental Protection Agency (U.S. EPA). 2022. EPA ExpoBox (A Toolbox for Exposure Assessors). United States Environmental Protection Agency, Washington, DC, USA. Available at: https://www.epa.gov/expobox.

U.S. FDA (U.S. Food and Drug Administration)
U.S. Food and Drug Administration (U.S. FDA). 2020. Use of International Document ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process." United States Food and Drug Administration, Silver Spring, MD, USA. Available at: https://www.fda.gov/media/85865/download.

California Office of Environmental Health Hazard (OEHHA)
California Office of Environmental Health Hazard Assessment (OEHHA). Proposition 65 Website. Available at: https://oehha.ca.gov/proposition-65.

California Office of Environmental Health Hazard Assessment (OEHHA). Initial Statement of Reasons Title 27, California Code of Regulations, Proposed Amendment to Section 25703, Subsection (a)(6) Quantitative Risk Assessment, Safe Drinking Water and Toxic Enforcement Act of 1986 Proposition 65. Available at:
https://oehha.ca.gov/media/downloads/crnr/072911isor25703.pdf.

California Office of Environmental Health Hazard Assessment (OEHHA). 2001. Process for Developing Safe Harbor Numbers. Available at: https://oehha.ca.gov/media/downloads/crnr/2001safeharborprocess.pdf.

California Office of Environmental Health Hazard Assessment (OEHHA). California Proposition 65 Glossary. Available at: https://www.p65warnings.ca.gov/glossary.

California Safe Drinking Water and Toxic Enforcement Act of 1986. Available at: https://govt.westlaw.com/calregs/Browse/Home/California/CaliforniaCodeofRegulations.

3 Definitions and Abbreviations

3.1 Definitions

The following definitions shall apply in this document:

Consumer Information - Warnings, directions for use, ingredient lists, and nutritional information. “Consumer information” as it relates to Proposition 65 does not include the brand name, product name, company name, location of manufacture, or product advertising.

Consumer Product - Any article, or component part thereof, including food, which is produced, distributed, or sold for the personal use, consumption, or enjoyment of a consumer.

Consumer Product Exposure - An exposure that results from a person's acquisition, purchase, storage, consumption, or any reasonably foreseeable use of a consumer product, including consumption of a food.

Chronic Exposure - Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species).

Exposure - Coming into contact with a substance, for example by swallowing, breathing, or touching the skin or eyes.

Exposure Assessment - The process of estimating or measuring the magnitude, frequency and duration of exposure to an agent and the size and characteristics of the population exposed (U.S. EPA 2019b).

Hazard - Is a characteristic of a chemical that defines its potential to cause harm or adverse effects in humans. Hazard is the potential for harm.

Genotoxic - A term used when a chemical is able to interact with and damage the genetic material, DNA, of a cell, often causing a mutation. The tests that are used to assess the potential of a chemical to damage DNA are known as “genotoxicity” studies.

Leachate - Any liquid that, in the course of passing through matter, or being in contact with matter, extracts soluble or suspended solids, or any other component of the material through which it has passed or come into contact with.

Mutation - A heritable change in the structure or sequence of the DNA that carries the "blueprint" for the normal function of a cell, and which changes the function or behavior of the cell.

Developmental toxicant - An agent that causes developmental toxicity. A chemical that causes adverse effects on the developing embryo, fetus, or child resulting from exposure during or before pregnancy. Developmental toxicity, therefore, occurs when a chemical causes adverse effects on the developing embryo, fetus, or child resulting from exposure during or before pregnancy.[2]

Label - A display of written, printed or graphic material that is printed on or affixed to a product or its immediate container or wrapper.

Labeling - Any written, printed, graphic, or electronically provided communication that accompanies a product, such as a package insert.

Reproductive toxicant - An agent that can cause reproductive toxicity. Reproductive toxicity occurs when a chemical interferes with the ability to produce normal, healthy offspring. This includes effects on the female and male reproductive systems, and effects on the developing embryo, fetus, or child, resulting from exposure during pregnancy. Under Proposition 65, "reproductive toxicity" includes "developmental toxicity," "female reproductive toxicity," and "male reproductive toxicity".[3]

Safe Harbor Levels - A level of exposure to a listed chemical that does not require a Proposition 65 warning. A business does not need to provide a warning if exposure to a chemical occurs at or below these levels. These safe harbor levels consist of No Significant Risk Levels (NSRLs) for chemicals listed as causing cancer and Maximum Allowable Dose Levels (MADLs) for chemicals listed as causing birth defects or other reproductive harm.

Note:

(1) Definition Retrieved December 1, 2020, from: https://www.p65warnings.ca.gov/faq/businesses/what-are-safe-harbor-numbers

(2) The Proposition 65 list is updated by OEHHA in an ongoing basis. The reference to the Proposition 65 list in this document refers to the current Proposition 65 list. A copy of the current Proposition 65 list can be found at https://oehha.ca.gov/proposition-65/proposition-65-list/.

Safe Harbor Warning - A clear and reasonable warning that provides a "safe harbor" against enforcement actions for businesses that choose to use them.

Schematic - Technical drawing of an object that shows the relationship or order of assembly of various parts.

Significant Exposure - Exposure which occurs at a level greater than a safe harbor level (exposures high enough to require a warning).

[2] https://www.p65warnings.ca.gov/glossary#letter_d
[3] https://www.p65warnings.ca.gov/glossary#letter_r

Systemic Effects - Health effects that occur in tissues distant from the site of contact between the body and the toxicant.

Toxicity - The characteristic of being toxic or poisonous.

Drinking Water Treatment Unit Documents - Series of documents used for evaluation of drinking water treatment units which include NSF 42, 44, 53, 55, 58, 60, 61, 62, and 401.

3.2 Abbreviations

The following abbreviations apply in this document:

DWTUS — Drinking Water Treatment Unit Documents

BOM — Bill of Materials

CAS — Chemical Abstracts Service

PMI — Product Material Information

MADL — Maximum Allowable Dose Levels

NSRL — No Significant Risk Levels

OEHHA — California Office of Environmental Health Hazard Assessment

OECD — Organization for Economic Co-operation and Development

U.S. EPA — United States Environmental Protection Agency

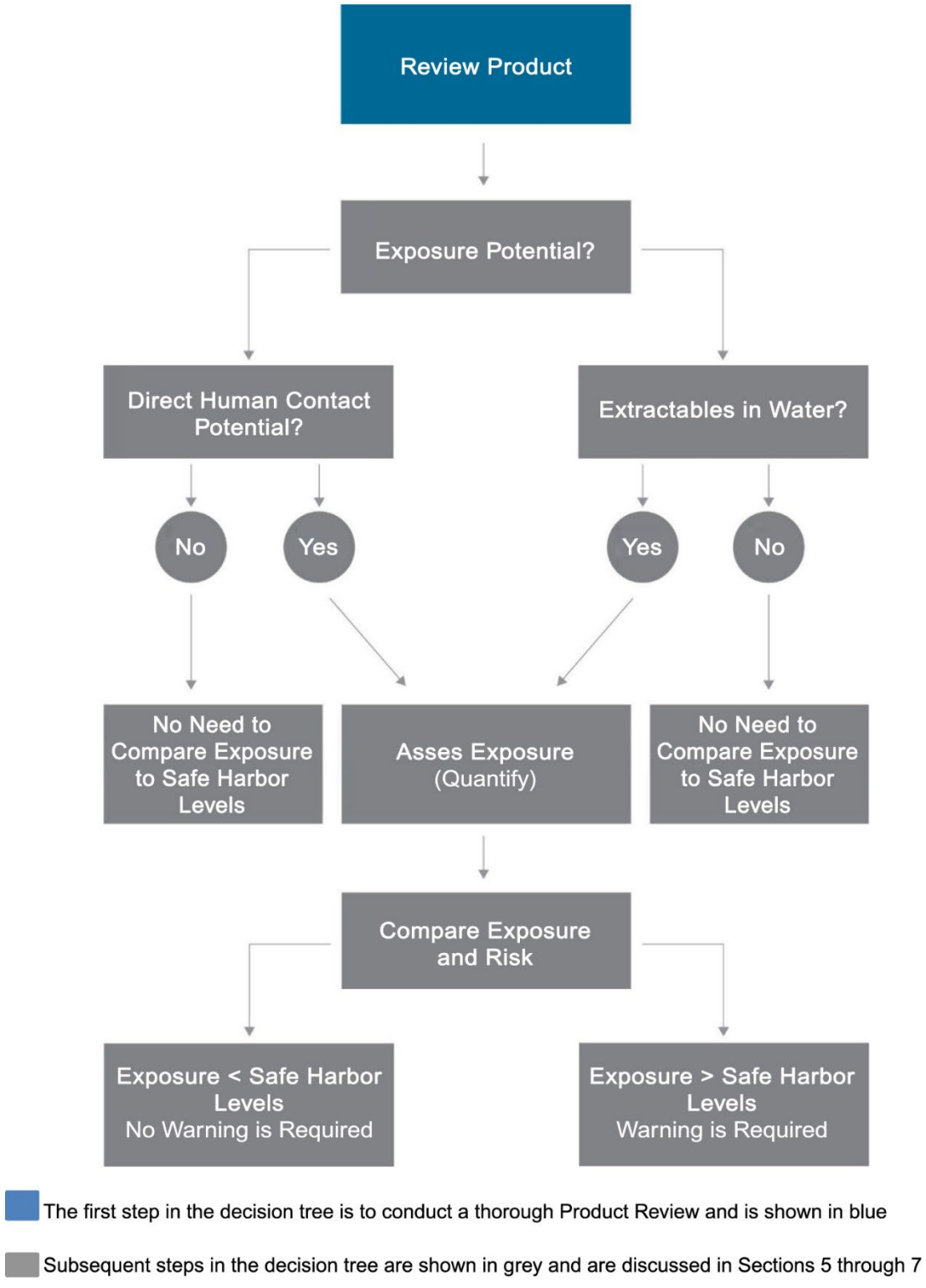
ICH — The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

4 Determining Conformance with California Proposition 65 Requirements

4.1 Decision Tree Approach for Determining Product Conformance with California Proposition 65 Requirements

Figure 1 outlines a decision tree for a risk assessor to use to determine if a product/material conforms to California Proposition 65 warning requirements. The decision tree asks a series of questions to drive the process for product conformance determination. The first step in the decision tree is to conduct a thorough Product Review and is shown in blue. Section 4.2 through Section 4.4 address the steps in the Product review process. Subsequent steps in the decision tree are shown in grey and are discussed in Section 5 through Section 8.

Figure 1
Determination of Product Exposure Compared to Safe Harbor Levels
(See Section 4)



4.2 Review Product Composition

In order to determine if a product/material complies with California Proposition 65 requirements, a determination of the complete chemical composition of a product is required. The following product information shall be obtained and reviewed (please refer to Appendix A for an example questionnaire and Appendix B for an example Product Materials Information (PMI) or Bill of Materials (BOM) form used to obtain the required information):

(a) Model Number and Name of Product
  (i) If the product is used to represent other, similar products, the justification for product "bracketing" shall be included in the documentation.
(b) Information about the Product manufacturer (i.e., company name, address, phone number, and point of contact)
(c) Information about the Product supplier(s) (i.e., supplier company name, address, phone number, and point of contact)
(d) Complete chemical composition of the Product (e.g., common name for each chemical, corresponding CAS numbers, percent composition of each chemical in the product, supplier information for each material/component)
(e) Diagram/Drawing/Photograph/Schematic of the Product to be evaluated, including a blown-out diagram to show all components.
(f) Manufacturer Instructions
  (i) Intended Use of Product
  (ii) Intended Frequency and Duration of use of the Product.
  (iii) Conditions under which the Product will be used (e.g., maximum temperature to which the product is exposed during its intended use, residential or occupational use)
  (iv) In-service lifetime of the Product.
(g) Information about how the Product is sold and/or given away (i.e., online, in-store, outside sales)
(h) Installation instructions (e.g., by a professional, by a consumer)
(i) Complete list of replacement part(s) for the Product
  (i) Installation instructions for replacement part(s)
(j) Information about any surface coating applied to the Product.
  (i) Chemical formulation for the surface coating
  (ii) Information about how the surface coating is applied.
    (1) In the field application information
    (2) In the factory application information
  (iii) If there is a surface coating, will it wear off over time, exposing the underlying surface?
(k) Any other information deemed necessary to conduct a complete Product review.

4.3 Material Specific Analysis

The purpose of obtaining the documentation in Section 4.2 is to identify the presence of Proposition 65 listed chemicals that would require further assessment. Specific testing and the method for exposure assessment, if necessary, shall be determined by the intended use and the chemical composition of the product provided by the manufacturer. If further assessment is recommended based on the initial Product review, the most rigorous conditions by which the product is typically used and handled shall apply. If a product is used under multiple conditions, the condition that may incur the highest level of exposure should be considered.

4.4 Proposition 65 Chemical Analysis

After the initial product review, the chemical composition of the product, shall be compared to chemicals on the most current Proposition 65 list. Chemicals considered would be those that are intentionally added to the product, those known to be present in a product. If ingredients are not on the Proposition 65 list, no further assessment is required, and no Proposition 65 warning is required. If any ingredients are determined to be on the Proposition 65 list, an exposure assessment may be conducted (see Section 5).

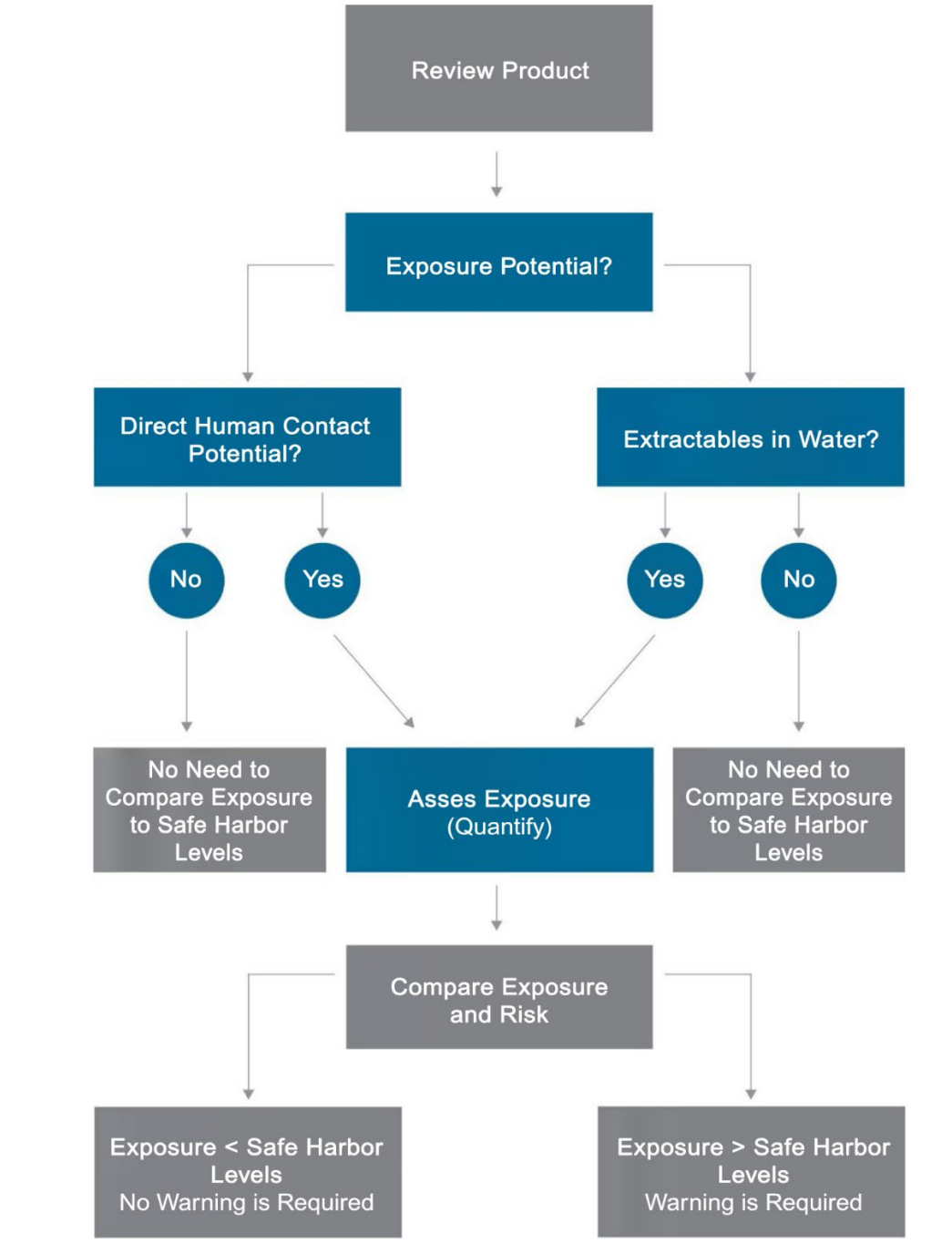
5 Exposure Assessment

After the initial product review and comparison of ingredients to chemicals on the Proposition 65 list, an exposure assessment may need to be conducted to determine if further analysis is needed. According to the California Code of Regulations, exposure is defined as “coming into contact with a substance, for example by swallowing, breathing, or touching the skin or eyes.”

If product ingredients are on the Proposition 65 list, but no human exposure potential exists, no further assessment is required, and no warning Proposition 65 warning is required. However, if a product’s ingredients are on the Proposition 65 list and there is the potential for human exposure, an exposure assessment is warranted.

With respect to this Document, the purpose of the exposure assessment is to estimate the type and magnitude of actual/estimated exposures and the route by which humans may be exposed to the chemical ingredient(s) of a product/material, if product ingredient(s) are on the Proposition 65 list. The steps for conducting an exposure assessment are outlined in Sections 5.1, 5.2, and 5.3. The exposure assessment steps are shown in blue on the decision tree in Figure 2. For more detailed information on exposure assessments, please refer to Guidelines for Human Exposure Assessment (U.S. EPA 2019b) and the Exposure Factors Handbook (U.S. EPA 2011 and U.S. EPA 2019a).

Figure 2
Exposure Assessment Steps
(See Section 5)



5.1 Characterize the Exposure Setting and Determine Exposure Potential

The exposure setting, both the physical environment and the potentially exposed population must be defined by the risk assessor as an initial step in the exposure assessment and are dependent upon the intended use of each product. Information obtained from the initial product review step will inform the risk assessor as to the exposure setting for a specific product (e.g., a water filtration device might be used on a kitchen faucet and use of the product will expose anyone who uses water from the faucet after filtration). A risk assessor must take into account potential vulnerable and more susceptible groups and populations. When appropriate, risk assessors evaluate unique characteristics and sociodemographic factors that may increase vulnerability such as sex, genetic variation, behaviors, race/ethnicity, lifestyle, culture, diet, and daily activities. In general, the risk assessor should use most realistic exposure scenario to determine dose. Exposure potential is dependent upon whether an exposure pathway is complete in a particular exposure setting, either by direct contact with a toxicant in a product or by contact with chemicals that are released from the product into water or air. Exposure may occur to a product and in some cases, product packaging. If exposures to a listed chemical from the product packaging are determined to occur, those exposures should be further evaluated (i.e., quantified) and considered together with exposures to that same chemical from the product itself.

5.2 Identify Exposure Route(s)/Exposure Pathways

After the exposure setting has been determined, a risk assessor must evaluate the setting to determine if any exposure pathways may be complete by any route of exposure. According to Title 27 of the California Code of Regulations:

§ 25707. Routes of Exposure

"Where scientifically valid absorption studies conducted according to generally accepted documents demonstrate that absorption of a chemical through a specific route of exposure can be reasonably anticipated to present no significant risk of cancer at levels of exposure not in excess of current regulatory levels, the lead agency may identify the chemical as presenting no significant risk by that route of exposure. Any exposure, discharge or release of a chemical so identified shall be deemed to present no significant risk to the extent that it results in exposure to humans by the identified route, and does not exceed the level established in any other applicable federal or state document, regulation, guideline, action level, license, permit, condition, requirement or order.

The following chemicals present no significant risk of cancer by the route of ingestion:

(1) Asbestos

(2) Beryllium and beryllium compounds

(3) Cadmium and cadmium compounds

(4) Nickel and nickel compounds

5.2.1 Mode of Contact Review

The exposure assessment should include an evaluation of the different potential modes of contact (routes of exposure), both direct and indirect to determine if any of the exposure pathways are complete. There are three basic modes of contact, and the degree or extent of exposure is determined by measuring/estimating the amount of a toxicant at the point of contact. The three basic modes of contact are ingestion, inhalation, and direct contact (dermal) and are discussed in Section 5.2.1.1 through Section 5.2.1.3. Exposure doses should be expressed as µg/day so they can be directly compared to safe harbor levels.

5.2.1.1 Ingestion Exposure

Ingestion exposure occurs when an individual introduces a chemical into the gastrointestinal tract, either intentionally or unintentionally. A chemical may interact with the gastrointestinal tract or may be absorbed into the bloodstream. In an exposure assessment, the ingestion of both food and non-food items must be taken into account which may include an understanding of oral exposure to vapors or air concentrations of chemicals, and chemicals in dust, soil, and other non-food items (U.S. EPA 2019b). Ingestion is, for most of the products/materials within the scope of this Document (e.g., drinking water treatment products, plumbing products, drinking water treatment chemicals) the most likely exposure pathway typically leading to the highest dose. The ingestion exposure dose is equal to the concentration of the chemical in water or other media multiplied by the ingestion rate. A general equation for estimating the ingestion dose is shown below (U.S. EPA 2019b):

$E_{ing} = C_{ing} \times IR$

Where:

E_{ing} = ingestion exposure dose (µg/day)
C_{ing} = concentration of the chemical of interest in water or other media (e.g., µg/L)
IR = ingestion rate (e.g., L/day)

OEHHA does not specify which ingestion rate should be used; therefore, it is recommended that U.S. EPA (2019a) be used as a source of information about ingestion rates.

5.2.1.2 Direct Contact (Dermal) Exposure

Direct contact exposure occurs when a chemical contacts an individual's skin (e.g., while swimming, bathing, showering, gardening). A chemical may act directly on the skin or may be absorbed through the skin to act systemically. A dermal exposure evaluation includes an assessment of what components of a product are readily handled by a consumer. This mode of contact review should consider whether a component is internal to a product, where an individual does not come in contact, or whether a component of the product is external, where direct contact can occur. Dermal contact may also be considered if a component is exposed to water when leaching or extraction may occur, and that water containing a compound can either be in direct contact with skin, or have an air vapor or air concentration, which comes into contact with skin. Dermal exposure dose is equal to the concentration or mass of chemical in the medium contacting the skin. A general equation for estimating dermal exposure is shown below (U.S. EPA 2019b):

$E_{derm} = MR_{medium} \times C \times SA$

Where:

E_{derm} = dermal exposure dose (mass per time)
MR_{medium} = mass of medium contacting the skin per time (mass of medium per skin surface area per time)
C = average concentration in medium (mass of chemical per mass of medium)
SA = skin surface area available for contact (area)

OEHHA does not specify which skin surface area should be used; therefore, it is recommended that U.S. EPA (2011) be used as a source of information for skin surface area.

5.2.1.3 Inhalation Exposure

Inhalation exposure occurs when an individual breathes a chemical. Depending on chemical properties, a chemical can cause point-of-entry effects by directly affecting the respiratory tract or the chemical may enter the bloodstream through respiratory tract tissues and potentially cause systemic effects. Due to the complex nature of the respiratory tract, estimating the inhaled dose is complicated (U.S. EPA 2019b). With respect to this Document, inhalation exposure involves the breathing of any chemicals a product may release into the air or vapor, or through water that carries a leachate/extractable that vaporizes and is then inhaled. The inhalation dose for a given exposure event is equal to the average chemical concentration in the air in a person's breathing zone multiplied by the inhalation rate (U.S. EPA 2019b):

$E_{inh} = C_a \times IR$

Where:

E_{inh} = inhalation exposure (mass per time)
C_a = airborne concentration of the chemical contacted by the exposed individual (mass of chemical per volume of air in breathing zone)
IR = inhalation rate (volume of air breathed per unit time)

OEHHA does not specify which inhalation rates should be used; therefore, it is recommended that U.S. EPA (2011) be used as a source of information for inhalation rates.

5.2.2 Combined Exposure

Combined exposure is the total exposure to a chemical due to ingestion, inhalation, and dermal routes of exposure and is additive and accounted for through a summation of the various exposure amounts. In some cases, a specific health effect (e.g., reproductive effects) only occur through one route of exposure (e.g., reproductive effects only occur via the ingestion route but not the dermal or inhalation routes). Proposition 65 evaluations are conducted on a chemical-by-chemical basis. Combined exposure may be determined by summing the E_{ing}, E_{inh}, and E_{derm} as shown in the equation below:

$E_{total} = E_{ing} + E_{inh} + E_{derm}$

Where:

E_{total} = total exposure dose from all exposure pathways (µg/day)
E_{ing} = ingestion exposure dose (µg/day)
E_{inh} = inhalation exposure dose (µg/day)
E_{derm} = dermal exposure dose (µg/day)

5.2.3 Default Body Weights Used to Determine Daily Dose

The body weights for humans recommended by OEHHA include (in units of kilograms):

70 kg - Adult male
58 kg - Adult female
58 kg - Adult female with conceptus
40 kg - Adolescent (age 11-18 years)
20 kg - Child (age 2-10 years)
10 kg = Infant (age 29 days-1 year)
3.5 kg = Neonate (age 0-28 days)

5.3 Laboratory Analysis/Modeling Methods Used to Quantify Exposure Concentrations

Once an initial product composition review has been conducted, and the exposure assessment for ingredients on the Proposition 65 list has been conducted and found at least one exposure pathway to be complete, a risk assessor may choose to quantify what levels of a chemical an individual may be exposed to by conducting laboratory analyses/modeling. The types of testing/modeling required will depend on the product being evaluated and the possible exposure scenarios (e.g., inhalation, dermal contact, and ingestion). The exposure quantification steps (laboratory analyses/modeling) are shown in blue on the decision tree in Figure 3.

Note: *For Proposition 65 settlements (Settlement Judgments) testing in accordance with the settlement shall be followed. For evidence of enforcement see a list of settlement judgments which are included in Appendix C*

5.3.1Types of analytical testing available for products/materials

The type of analyses required for a product will be based on the chemicals requiring further assessment. Article 9 of Title 27, California Code of Regulations provides guidance regarding the use of specific methods of detection and analysis, where "methods of detection and analysis" defined in Article 9 is a "specific analytical testing procedure appropriate for detecting a particular chemical in a particular matrix such as air, water, soil or food that is applied for the purpose of detecting the chemical or measuring its concentration." "Matrix" is defined as "the component or substrate that contains the chemical." According to Article 9:

- The method of detection and analysis should be "conducted by a laboratory certified by the State of California or accredited by the State of California, a federal agency, the National Environmental Laboratory Accreditation Program or similar nationally recognized accrediting organization to perform the particular method of detection and analysis in question."
- The method of detection and analysis should be applied to the same matrix in which the exposure is likely to occur (e.g., air, water, soil, or food).
- The methods of detection and analysis that may be used are those that are "required or sanctioned by the federal Food and Drug Administration, the U.S. Environmental Protection Agency, the federal Consumer Product Safety Commission, the California Department of Health Services, the California Environmental Protection Agency and its constituent boards, departments or office, an Air District, a Regional Water Quality Control Board, a Certified Unified Program Agency, or other local enforcement agency in California with jurisdiction over the product…"

Please refer to Appendix D for information regarding testing methods.

5.3.2 Models that can be used to estimate exposure concentrations

Modeling can be used to estimate exposure concentrations, either in combination with laboratory testing or without. When used together with analytical testing, and a dose concentration in water (if relevant) data can be taken from the testing, it can be used to determine if there is significant ingestion exposure, and also if there is a relevant concentration of a chemical that can be leached or extracted and expose an individual by either

(a) direct contact with the user or consumer (dermal route of exposure), or
(b) release into water or off-gas at a concentration that an individual can inhale (inhalation route of exposure).

Models can be used without analytical testing by using indirect estimation of exposure concentrations. Indirect estimation is typically not as accurate as using analytical data to predict exposure. Whether being used alone or in combination with analytical testing, some models may be useful to use to estimate dose or concentration upon exposure, one useful tool for this can be the EPA model EPI Suite. Details of the EPI Suite are beyond the scope of this Document but can be accessed to review in more detail here: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Human exposure can occur in one of three routes or in a combination of these routes: oral, inhalation, and dermal. Another great tool is the EPA Expobox which can help provide guidance on how to decide the appropriate approaches, consideration for media, and methods or models for the three routes of exposure: https://www.epa.gov/expobox.

For the practicing risk assessor, the EPA updated their guidance on human exposure assessment in 2019 and that guidance can be accessed here: https://www.epa.gov/risk/guidelines-human-exposure-assessment. Section 2.6 includes a list of exposure models that may be useful in the quantification of exposure.

These resources can include guidance on addressing uncertainty in the exposure assessment as well. EPA guidance addresses some of this, including Bayesian analysis. Another useful resource for comparison for extractables and leachates includes FDA guidance on medical devices, which relates to the ISO 10993-1 Document. The guidance can be accessed here: https://www.fda.gov/media/85865/download.

6 Identification/Derivation of Safe Harbor Levels for Chemicals on the Proposition 65 List

Once exposure pathways for a Product have been identified and any exposure that might occur has been quantified (see Section 5 of this Document), the next step in the Proposition 65 evaluation process involves identification of an existing Safe Harbor Level, or derivation of a Safe Harbor Level for the chemical(s) in the product. Proposition 65 is limited to consideration of two general types of toxicity, cancer and reproductive/developmental toxicity. Thus, Safe Harbor Levels that exist under Proposition 65, or that might need to be derived in order to comply with Proposition 65 warning requirements, only relate to one of those two endpoints of toxicity. The Safe Harbor Levels associated with Proposition 65 are known as “No Significant Risk Levels” (NSRLs) for carcinogens and as “Maximum Allowable Dose Levels” (MADLs) for reproductive/developmental toxicants. The California Office of Environmental Health Hazard and Assessment (OEHHA), the regulatory authority that implements Proposition 65 in California, maintains a list of chemicals that the State has identified as either carcinogens or reproductive toxicants. Chemicals are first listed and then, in some cases, OEHHA has derived NSRL or MADL levels for a listed chemical; in other cases, the chemical may never have a defined Safe Harbor Level.[4] This Document for certain products addresses both situations that might be encountered by risk assessors.

[4] Chemical get listed by OEHHA as Proposition 65 chemicals through one of four mechanisms: 1) Labor Code listings; 2) Formally Required to be Listed; 3) Authoritative Bodies (*i.e.,* IARC, EPA, FDA); or 4) State Qualified Expert Committees.

6.1 Decision Tree Approach for Identifying Safe Harbor Levels

Figure 3 and Figure 4 outline a decision tree approach for a risk assessor to use when identifying Safe Harbor Levels that can be employed for making Proposition 65 warning decisions. The decision tree asks a series of questions to drive the process for Safe Harbor Level identification, specifically NSRLs in Figure 3 and MADLs in Figure 4. Moving through the decision tree, a risk assessor will be either identifying that a NSRL or MADL exists for the chemical of interest or, if such values are not already listed by OEHHA, the risk assessor will be determining if a NSRL or MADL can be derived.

Key points in the decision tree for cancer risk include the following (Figure 3):

(a) A risk assessor finds that exposure to a listed chemical occurs.
(b) A risk assessor finds that the chemical is not listed by OEHHA as a carcinogen (go to the red box in the decision tree) which means that no Proposition 65 warning is required for cancer effects;
(c) A risk assessor identifies a chemical listed as a carcinogen and also finds that OEHHA has identified a Safe Harbor Level (NSRL) such that comparison to exposure levels must be performed to make a warning decision for the chemical; and
(d) A risk assessor identifies a chemical listed as a carcinogen and finds that OEHHA has not identified a Safe Harbor Level (NSRL), which leads to the need to derive a NSRL for that chemical.

Key points in the decision tree for reproductive/developmental risk warning (Figure 4):

(a) A risk assessor finds that exposure to a listed chemical occurs;
(b) A risk assessor finds that the chemical is not listed by OEHHA as a reproductive/developmental toxicant (go to the red box in the decision tree) which means that no Proposition 65 warning is required for reproductive/developmental effects;
(c) A risk assessor identifies a chemical listed as a reproductive/developmental toxicant and also finds that OEHHA has identified a Safe Harbor Level (MADL) such that comparison to exposure levels must be performed to make a warning decision for the chemical; and
(d) A risk assessor identifies a chemical listed as a reproductive/developmental toxicant and finds that OEHHA has not identified a Safe Harbor Level (MADL), which leads to the need to derive a MADL for that chemical.

It is important to remember that for some chemicals, they have been listed by OEHHA as both carcinogens and as reproductive/ developmental toxicants. In those cases, both decision trees would apply, and a risk assessor would need to perform assessments for both types of toxicity. Additionally, risk assessors should only derive NSRL and MADL values on their own if they have the training and qualifications to do so (*e.g.*, toxicology, epidemiology, physiology, medicine). The Document does provide a risk assessor with some tools to use when assessing the quality of a NSRL or MADL assessment that either already exists, or that might be performed at their request.

Figure 3
Cancer Risk Warning
(See Section 6.1)

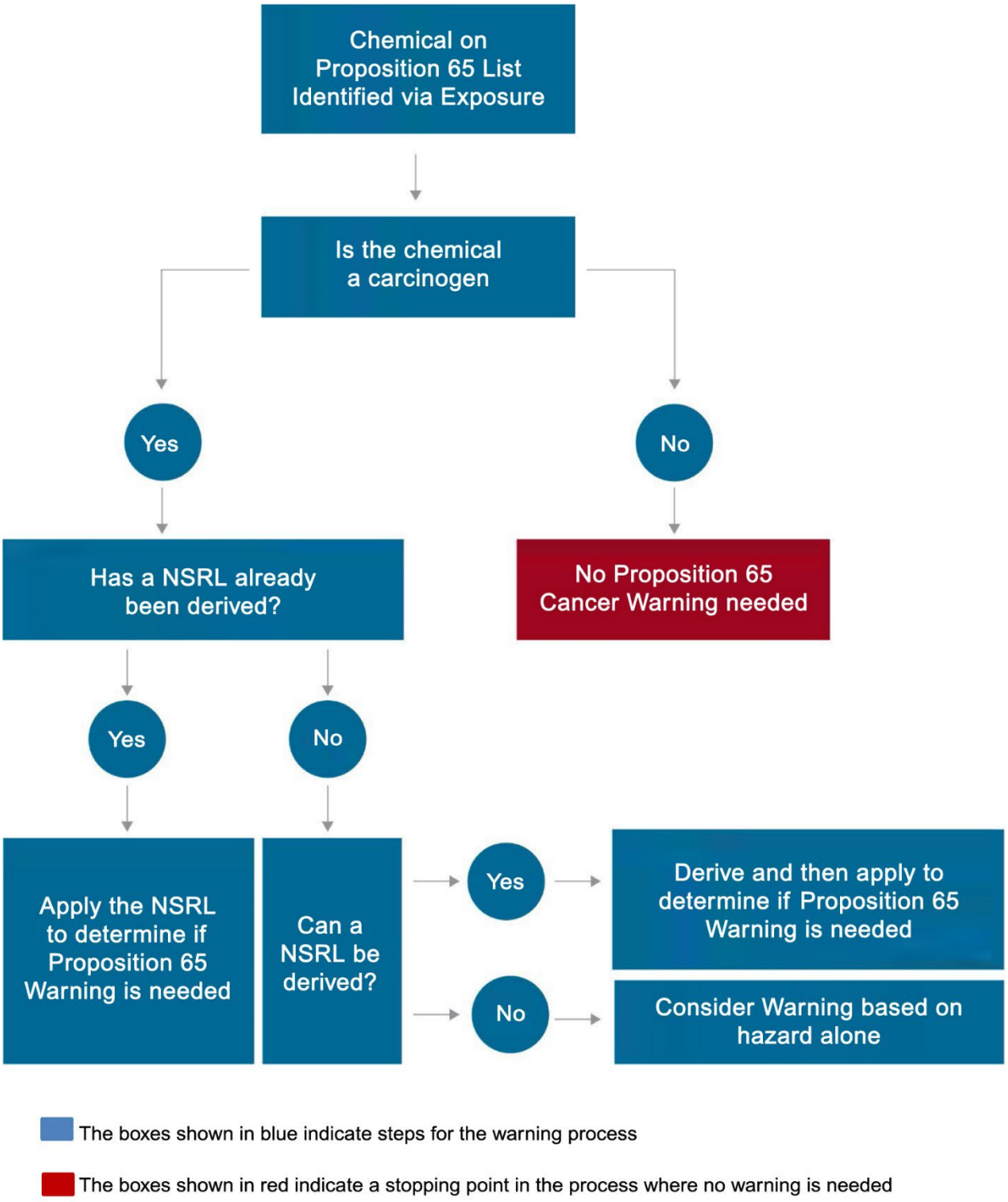
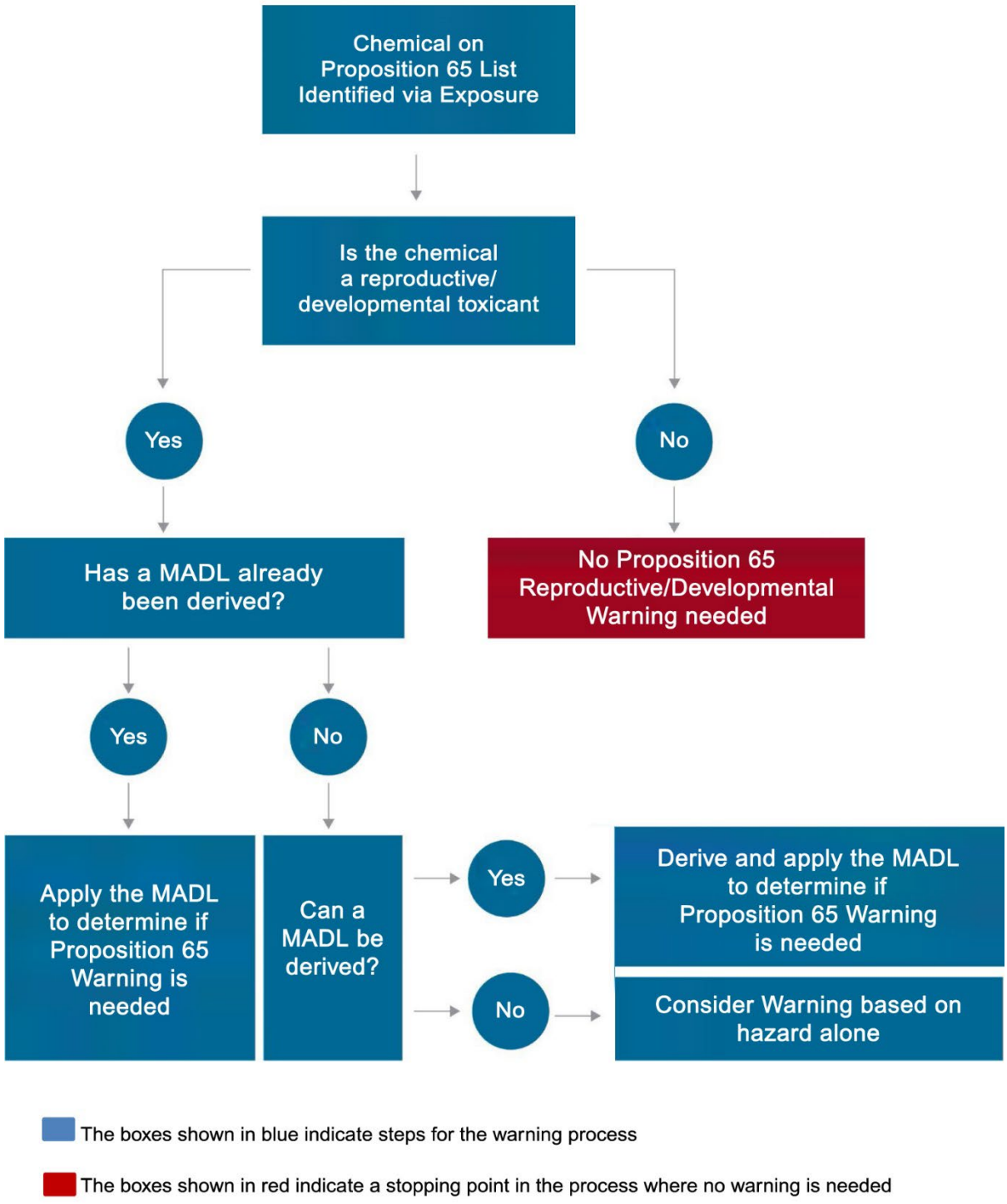


Figure 4
Reproductive/Developmental Warning
(See Section 6.1)



6.2 NSRL Values for Carcinogens

A NSRL represents the *"levels of exposure 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)"* (OEHHA, 1989[5]). In Figure 3, the first basic question asks whether there is exposure to a chemical in the product that is on the Proposition 65 list. Only if there is a potential for exposure will there be a need to take further steps (Figure 3). Once exposure is identified, the OEHHA list should be used to guide the decision tree finding of whether a compound is a carcinogen. It is important to remember that OEHHA's list of carcinogens is developed based on knowledge available to date and changes over time as new scientific information becomes available or as authoritative bodies perform reviews and list compounds[6]. As a result, risk assessors need to revisit the Proposition 65 listings on a routine basis to see if a chemical in their products has been listed or removed from existing listing.

For chemicals that are identified as carcinogens, and for which there is a potential for exposure the next point in the decision tree asks if there is a NSRL that has already been derived and adopted into regulation, following California's rulemaking process by OEHHA. A list of NSRLs is available on the OEHHA Proposition website[7]. If one is available, then that NSRL would be used during a exposure comparison to Safe Harbor Levels in Section 7 of the Document. Although the Proposition 65 list includes a listing of many different chemicals, not all carcinogens have NSRLs. If the chemical of interest is listed as a carcinogen without a listed NSRL, the next step in the decision tree asks if one can be derived. As already discussed, only qualified personnel should undertake NSRL derivation. The next section gives some guidance on the principles to be applied during NSRL derivation as well as some guidance for the risk assessor that needs to assess the quality of work performed at their request.

6.2.1 Derivation of NSRL Values: Issues to Consider

A NSRL is an intake value for a chemical, expressed in units of µg/day. Thus, the first step for deriving a NSRL set forth by OEHHA[8] involves derivation of a cancer potency factor using methods similar to methods used by other regulatory authorities such as the U.S. EPA (2005)[9]. A cancer potency factor is a quantitative assessment of cancer risk. As already discussed, cancer risk is a level that is linked with no more than 1 case of cancer being associated with exposure to the chemical within a population of 100,000 people (OEHHA's standard). This value, also expressed as the 10E-05 risk level, is then divided by the slope factor, expressed in units of one divided by milligram (mg) per kilogram (kg) body weight per day. The result of the calculation is a dose level associated with a 10E-05 risk in units of mg/kg-day. This dose can then be converted to an intake amount in units of mg/day by multiplying the body weight for humans. When the calculation is for the general population, the body weight assumed to be 70 kg. The intake can then be converted to a µg/day amount by multiplying by 1000.

Common to both OEHHA and U.S. EPA methodology is the first step of evaluating the quality of available toxicological data, which can include data collected in animals or in human populations. The available studies are used to identify the critical effect of the chemical, in this case carcinogenicity potential. In this data evaluation process, OEHHA guidance assumes that

[5] https://oehha.ca.gov/media/downloads/crnr/072911isor25703.pdf
[6] The Proposition 65 warning requirement takes effect one year after a chemical is listed.
[7] https://oehha.ca.gov/proposition-65/proposition-65-list
[8] Title 27 California Code of Regulations, Article 8
[9] https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

there is no threshold below which there is no risk of cancer. As a result, OEHHA derives NSRLs through use of no-threshold models (extrapolation down to no exposure in a straight line, known as low dose linear extrapolation). In the final step, the NSRL derived will be compared to exposure estimates for a population. If the exposure estimates are at or lower than the NSRL, then the exposure to the population is considered acceptable if it is within a margin of safety, or a risk that does not exceed a risk of greater than 1 in 100,00 (Title 27 California Code of Regulations, Article 8).

Evaluation of the quality of the available data is a key or critical step in the process of NSRL derivation. A weight-of- evidence evaluation is typically used. Evidence considered in the process typically would include data on tumor findings, or lack of such data, in humans and laboratory animals; an agent's chemical and physical properties; a chemical's structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Much of this evidence is first evaluated as part of the hazard identification process in risk assessment. Although data from human studies (i.e., epidemiologic or clinical studies) are generally preferred for characterizing human cancer hazard and risk, all types of data and information could be employed as non-human data may provide insight into the possible mode(s) of action and likelihood of human cancer hazard and risk. Such an evaluation of data should only be undertaken by risk assessors that have training and/or experience in evaluating toxicological study data in animals as well as studies in human populations.

In some cases, there may be cancer risk assessments that have been performed by outside regulatory bodies (*e.g.,* EFSA, U.S. EPA, other U.S. state agencies) or even published in the peer-reviewed scientific literature. If that is the case, then risk assessors within companies should evaluate those risk assessment findings based on some key data quality factors that are commonly used in evaluation of carcinogenicity datasets.

These quality factors for animal studies would include the following:

(a) the study was conducted under Good Laboratory Practice (GLP)[10] conditions;
(b) the exposure has been adequately described and it is relevant to the way that humans might be exposed;
(c) the study was conducted for the lifetime of the animal with daily dosing;
(d) study groups included both exposed and unexposed animals and the groups were of sufficient size for statistical analysis;
(e) dose-response data was collected (multiple exposure groups versus only one); and
(f) background rates of tumor formation in the animal species and strain were considered and discussed, if relevant. Because of the need to ensure that quality data are being used in any cancer risk evaluation, guidelines for toxicology study design have been developed, including designs for carcinogenicity testing in animals.[11] These guidelines for animal study design can be used by a risk assessor when evaluating the quality of study data that may have been used to derive a NSRL. Adherence with these guidelines is preferred if animal data are being used as a basis for a NSRL value.

[10] GLP is a quality system concerned with the process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.
[11] https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-870-health-effects-test-guidelines

In addition to animal studies, human epidemiological study data may have been used to derive a NSRL. If so, a similar evaluation of study quality is appropriate. The quality factors for human studies would include the following:

(a) the study clearly articulates study objectives or hypothesis;
(b) there was proper selection and characterization of comparison groups (exposed and unexposed groups or case and control groups), and exposure is relevant to the assessment being performed (oral, versus dermal versus inhalation);
(c) exposure has been adequately characterized (quantified);
(d) the study had sufficient length of follow-up for disease occurrence;
(e) ascertainment of the causes of cancer morbidity and mortality in the study was adequately described;
(f) bias and confounding factors were considered;
(g) the sample size was adequate to detect an effect (power of the study);
(h) methodology for data collection and analysis was clearly described; and
(i) the study included complete and clear documentation of results. It is unusual for human studies to have all of these characteristics, and some are more critical than others. For example, inadequate description of exposure, both amount and duration, would be a limitation that could lead a risk assessor to exclude human data for NSRL derivation.

Also of concern would be studies that are not able to separate out exposures for specific chemicals; multiple types of exposures occurred, not just exposure to one chemical. A risk assessor should evaluate any NSRL derivation process based on human data with these quality factors in mind.

Although this Document is not meant to be a comprehensive discussion of issues associated with NSRL development, it is important for risk assessors to be familiar with the concept of "genotoxic potential" or "a genotoxic mode of action" for a chemical. The term "genotoxic" is defined as the ability of a chemical to interact with and damage the genetic material, DNA, of the cell. In some cases, the damage leads to a "mutation" in the DNA, where a mutation is defined as a heritable change in the structure or sequence of the DNA that carries the blueprint for the normal functioning of the cell, and which changes the cell's function. The functional change could be uncontrolled cellular proliferation (tumor formation). Chemicals that are carcinogenic may be classified as being genotoxic, although not all carcinogens produce cancer through direct genotoxic events or activity.

Toxicologists often perform a battery of genotoxicity studies for chemicals as a first step in defining the hazards linked to that chemical. Risk assessors may encounter chemicals that have robust datasets showing that a compound is genotoxic, while other chemicals may have a robust dataset showing it is not genotoxic. A lack of genotoxicity does not mean a chemical does not pose a cancer hazard. That is because there are chemicals that cause cancer by mechanisms other than through direct interactions with DNA. EPA has specific guidance that separates chemicals by this characteristic, mode of action for cancer by mechanisms other than direct genotoxicity, allowing for use of different methods for cancer risk assessment depending on whether a chemical is genotoxic, or not. For additional discussion of this issue, the EPA guidance documents are useful.[12]

[12] https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf

Risk assessors that follow the decision tree for carcinogens (Figure 3) will arrive at the point where they will either decide that no warning for cancer is needed or will find they need to move to the next step in the process, where the NSRLs are placed in the context of exposure potential.

6.3 MADL Values for Reproductive Toxicants

In the decision tree for reproductive/developmental toxicants (Figure 4), after considering whether exposure to a listed chemical occurs, and whether the chemical is listed as a reproductive/developmental toxicant (if not, the process stops at the red box), the next question asks if there is a MADL that already has been derived and adopted into regulation, following California's rulemaking process by OEHHA. If one is available, then the MADL would be used during comparison to an exposure estimate in Section 7 of the Document. Not all reproductive toxicants have MADLs published by OEHHA. If no MADL is listed, then the risk assessor needs to determine if there are data of sufficient quality for derivation of a MADL. As a result, for chemicals identified as reproductive toxicants but for which no MADL is available, the next decision tree point asks whether a MADL can be derived. As already discussed, derivation of a MADL value should only be undertaken by someone with the appropriate training and expertise, which may not be the risk assessor.

6.3.1 Derivation of MADL Values: Issues to Consider

OEHHA's guidance[13] sets forth its methodology for deriving MADL values. The U.S. EPA also has published guidance on assessing reproductive toxicity risk (U.S. EPA 2016[14]) and developmental toxicity risk (U.S. EPA 1991[15]). The science of risk assessment for chemicals with potential reproductive toxicity/developmental toxicity also employs a weight-of- evidence approach and requires a specific type of training and expertise for scientists that undertake evaluation of this type of human/animal study. Although U.S. EPA guidance addressed the topic of reproductive and developmental risk assessment separately, OEHHA's listing combines the two potential hazards under one warning statement, a statement that can be required based on the presence of only one of the two hazards, or both.

Common to both OEHHA and U.S. EPA methodology is the need to evaluate the quality of available toxicological data. Just as was described above for derivation of a NSRL, the available studies are used to identify the critical effect of the chemical, in this case the ability to induce birth defects (developmental toxicity) or to affect the ability of an animal to reproduce (reproductive toxicity). Since adverse effects on reproductive organs can affect fertility and the ability to reproduce, the potential of a chemical to affect both male and female reproductive organs and systems need to be evaluated. OEHHA guidance discusses the general principles to be applied in MADL development, principles that a risk assessor needs to understand whether they are relying on already published MADL values or is asking an outside expert to derive a MADL on their behalf. These principles are as follows (Title 27 California Code of Regulations, Article 8):

[13] Title 27 California Code of Regulations, Article 8
[14] https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf
[15] https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf

(a) The determination of whether exposure to a chemical poses the risk of reproductive and/or developmental toxicity is to be based on evidence that a level of exposure has no observable effect at one thousand (1,000) times the level of exposure in question. Thus, the risk assessor must determine the maximum dose level having no observable effect in a study and dividing that level by one thousand (1,000) to arrive at the maximum allowable dose level, the MADL.
(b) Only studies directed towards endpoints of reproductive and/or developmental toxicity provide the basis for the determination that a chemical is known to the state to cause reproductive and/or developmental toxicity.
(c) If there are multiple reproductive and/or developmental effects observed in a study chosen for use to derive a MADL, or if there are multiple studies available for review, the reproductive and/or developmental effect for which a study or studies produce the lowest No Observable Effect Level (NOEL) shall be utilized for derivation of the MADL (most sensitive endpoint).
(d) The NOEL shall be the highest dose level which results in no observable reproductive and/or developmental effects and should be expressed in milligrams of chemical per kilogram of bodyweight per day.
(e) The quality and suitability of available epidemiologic data shall be included in the assessment to determine whether the study is appropriate as the basis of an assessment considering such factors as the selection of the exposed and reference groups, the reliable ascertainment of exposure, and completeness of follow-up. Biases and confounding factors shall be identified and quantified.
(f) Animal studies, typically in rodents or rabbits, that are to be used for derivation of a MADL shall meet generally accepted scientific principles, including the thoroughness of experimental protocol, the degree to which dosing resembles the expected manner of human exposure, the temporal exposure pattern, the duration of study, the purity of test material, the number and size of exposed groups, and the route of exposure and the extent of occurrence of effects.
(g) The NOEL shall be based on the most sensitive study deemed to be of sufficient quality, either animal or human.
(h) The results obtained for the most sensitive study of sufficient quality for risk assessment shall be applicable to all routes of exposure for which the results are relevant. In other words, if the study is an inhalation study and humans would be expected to be exposed by inhalation, that needs to be considered when selecting a study for risk assessment purposes. If the only data available are inhalation exposure data, then anatomic, physiologic, pharmacokinetic, and metabolic considerations can be taken into account.
(i) When data do not allow the determination of a NOEL, the lowest observable effect level (LOEL) can be used by applying an additional factor of 10 (dividing by 10,000 rather than 1000) when deriving the MADL. Again, the resulting value is converted to a milligram per day dose level. If the MADL process is based on an adverse reproductive effect in a male, a human body weight of 70 kg (154 lbs.) shall be assumed. If the MADL process is based on an adverse reproductive effect in a female or on a developing organism (embryo, fetus), a human body weight of 58 kg (128 lbs.) shall be assumed.

6.3.2 Rare but relevant topics to consider

On occasion, an assessment can become complex if there is evidence that must consider limited data and evidence or circumstances that influence a calculation beyond what is required under normal guidance, this can include factors like:

(a) sensitive subpopulations (e.g., can be relevant to rare metabolizers of endocrine disruptors);
(b) animal data that are specific to a specific species or genetic strain of animals that do not have reproducible effects in other animal models or genetic strains when compared; and
(c) chemical specific factors like unique reactivity/formation of metabolites etc. that may be exposure route dependent as well (first pass metabolism in oral versus inhalation or dermal). Exploration of these types of scenarios as they would relate to NSRL or MADL derivation or evaluation are beyond the scope of this Document, but it is important for the risk assessor to be aware of the possibility.

Care should be taken when embarking on such analyses and should only be undertaken by a risk assessor with appropriate training and experience.

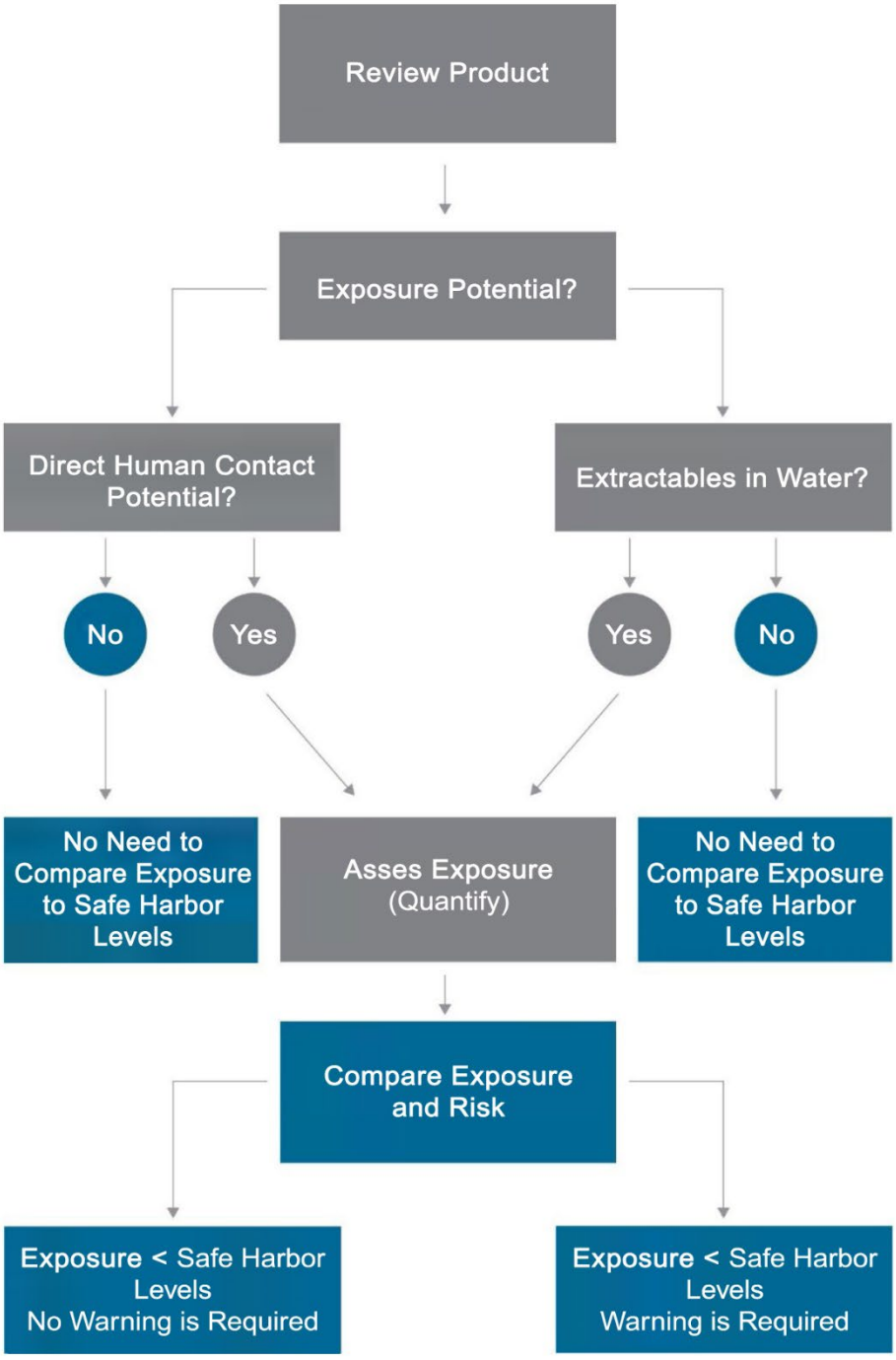
7 Exposure Determination as Compared to Safe Harbor Levels to Determine Product Compliance

7.1 Exposure Determination as Compared to Safe Harbor Levels - Outcomes

This Document focuses on characterizing any cancer risks and/or reproductive/developmental effects that have been identified for significant exposure to any of the known Proposition 65 listed chemical constituents of products. Although compliance with provisions of Proposition 65 can result in the need to provide warnings for products that have been identified as significantly exposing individuals to either carcinogens or reproductive/developmental toxicants, this Document does not provide labeling recommendations related to Proposition 65 more specifically, whether to label a product or not label with a warning statement. Such decisions are left to companies after they have used this Document to determine if any risks (cancer and/or developmental/reproductive) need to be addressed.

Figure 5 provides an overview of the information needed for an exposure determination compared to Safe Harbor Levels. The part of the figure that appears in blue is the focus of this step in the Document. The other parts of the figure that appear in gray were discussed in Sections 4, 5 and 6 of this Document.

Figure 5
Exposure Determination as Compared to Safe Harbor Levels - Outcome
(See Section 7)



The part of the figure that appears in blue relates to exposure determination compared to Safe Harbor Levels and is the focus of this step.

7.2 Establishing an Approach to Compare Exposure to Safe Harbor Levels

In this case, estimated exposure to the listed chemical from the product in question (in units of micrograms per day) is compared to the NSRL or MADL (in units of micrograms per day) to determine In Figure 5, if the estimate of exposure is found to be lower than the NSRL or MADL, then warning under Proposition 65 would not be necessary. If, however, exposure exceeds a Safe Harbor Level, then a company may need to consider the need to add a warning according to Proposition 65 requirements.

7.3 Product Labeling Guidance for Safe Harbor Warnings

At the time this IGC was finalized, information about the California Proposition 65 warning label requirements could be found at this webpage: https://www.p65warnings.ca.gov/. A safe harbor warning is deemed to be clear and reasonable by OEHHA and provides a safe harbor against enforcement actions for businesses that choose to use them. A business is not required to use the safe harbor warning methods and content. The safe harbor warning method is not applicable to products manufactured prior to August 1, 2018, nor is it applicable to companies covered by warning methods and content contained in a court-approved settlement. For information regarding safe harbor warnings provided on the internet and in catalogs, please refer to the Proposition 65 warnings webpage: https://www.p65warnings.ca.gov/.

A product manufacturer/supplier may need to provide a safe harbor warning in a language.

Appendix A
Example Proposition 65 Questionnaire

1. Company Name, Address, Contact Information:

2. Manufacturer Name, Address, Contact Information:

3. Please provide the following:
   (a) Diagram/Drawing/Photograph of Model
   (b) Complete chemical formulation
      (i) Include chemical names, CAS numbers, percent composition of each.
      (ii) Include supplier information for each component/material in the product as it was manufactured.
   (c) Laboratory toxicity test data, if available (e.g., NSF/ANSI 61 test data for a plumbing product)

4. Is the product currently certified to any Document associated with toxicity? Yes☐ No☐
   If yes, please provide details:

5. Product Information:
   (a) Model Number and Name:
   (b) What is the intended use of the product?
   (c) How long is product intended to be used?
   (d) How/Where is it sold? Online☐ Retail☐ Outside Sales Group☐
   (e) Is it installed by a professional ☐ or a consumer ☐?
   (f) If the product has replacement parts/components, how are they intended to be installed?
   (g) Does the product have a surface coating? Yes ☐ No☐ Please consider all surfaces that may come into contact with a person directly or indirectly (e.g., wetted area of a faucet or showerhead, bathtub surface, sink surface).
      If yes, please explain:
      (i) If so, how is coating applied?
         a. In the field Yes ☐ No☐
         b. In the factory Yes ☐ No☐
      (ii) Is there a possibility that the coating will wear off over time, potentially exposing an individual to the underlying surface? Yes ☐ No☐
         If yes, please explain:
   (h) If the product has a wetted surface, is there a surface treatment used? (e.g., lead wash) Yes☐ No☐
      If yes, please explain:

Appendix B
Example Product Material Information (PMI) Form

COMPANY NAME: _____
Model Number (Representative Sample): _____
Model Numbers (Bracketed Models):* _____

***Models are identical except for volume or aesthetic changes. Refer to bracketing form for additional information.**

NOTE: Shaded fields below are required only for evaluation against low lead criteria.

Complete this box if solder and flux are used in the product			
	Is it used? Yes/No	% Lead Content	Recognized Lab Findings for Lead Content
Solder			
Flux			

No.	Part Description	Part #	Quantity per assembly	Material	Supplier	Supplier Contact: Phone No. & email	External Surface (Dermal Contact Area) in^2	Aerosol Potential (Y/N)	Water Contact Area in^2	% Wetted Surface	% Lead Content in material	Weighted Lead Content	Recognized Lab Findings % Lead Content in Material
						Total:			0	0.00%	total:	0.0000	

The undersigned representative of the Company Certifies that the information provided is accurate and complete.

Signature: _____ **Date** _____
Print Name: _____ **Title:** _____
Company: _____ **Phone** _____

Appendix C
Proposition 65 Settlement Judgments

Case Documents:
Attorney General Settlements
https://oag.ca.gov/prop65/litigation

Annual Reports of Settlements
https://oag.ca.gov/prop65/annual-settlement-reports

Center for Environmental Health v. Katadyn North America, Inc
https://oag.ca.gov/system/files/prop65/judgments/2013-00237J2853.pdf

Appendix D

For chemicals of concern via the dermal route of exposure, an appropriate method of analysis will address the following:

Extraction (isolation of analytes) from product surface:
(a) Needs to be demonstrated that contaminant(s) may be removed easily and repeatably, and
(b) Needs to remove contaminant(s) efficiently (adequate recovery from surface).

Analysis:
(a) Appropriate analytical technique must be used, or one must be developed if an appropriate analytical technique is not available,
(b) Must be specific to the compound(s) in question, and
(c) Must be sufficiently sensitive.

Quality control:
(a) Demonstrate adequate detection limit,
(b) Demonstrate calibration,
(c) Recovery from the extraction matrix (matrix fortification and recovery), and
(d) Duplicate analysis.

For chemicals of concern via the ingestion exposure pathway, utilize exposure/extraction methods set in NSF/ANSI/CAN 61 and other Drinking Water Treatment Unit Documents (DWTUS) such as NSF/ANSI 42, 44, 53, 55, 58, 62, or 401. For Point-of-Entry water treatment product use NSF/ANSI/CAN 61 and for Point-of Use water treatment products use the applicable DWTUS.

For analysis of the chemicals not covered in NSF/ANSI/CAN 61 and other DWTUS use EPA or other recognized methods. Resources for methods that may be applicable:

- Document Methods for the Examination of Water and Wastewater, 23rd Edition.
- Test Methods for Evaluating Solid Waste: Physical/Chemical Methods, EPA SW-846 Compendium.
- Groundwater Testing: EPA 600/4-79-020 Series.
- Methods Approved to Analyze Drinking Water Samples to Ensure Compliance with Regulations: https://www.epa.gov/dwanalyticalmethods
- Methods to screen for residual chemical contamination on surfaces (e.g., bisphenol A residue (BPA) on component with BPA as an ingredient)
- Methods to screen for volatilization of chemicals into the air (e.g., off-gassing of a chemical ingredient).

APPENDIX E
Examples of NSRL and MADL Derivations

Situation Encountered:

An exposure assessment has been performed and it is likely that humans could be exposed to Compound Alpha[16] through drinking water (oral exposure) and/or bathing (dermal exposure). Derivation of a NSRL

Step 1: Is Compound Alpha Listed in the Proposition 65 List?
The risk assessor searches the current Proposition 65 to see if Compound Alpha is listed by the State of California as a Carcinogen (the Proposition 65 List) and finds Compound Alpha is listed but no NSRL has been derived by OEHHA.

Step 2: Do scientific studies and/or data exist that can be used to derive a NSRL for Compound Alpha?
The risk assessor searches sites where regulatory authorities list risk values that have already been derived for Compound Alpha focusing on risk values linked to cancer as a hazard. The sites to be searched would include those considered by OEHHA as authoritative bodies (i.e., the U.S. Environmental Protection Agency (U.S. EPA), the World Health Organization's International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), the National Institute for Occupational Safety and Health (NIOSH), and the U.S. Food and Drug Administration (U.S. FDA)). Other sites that should be considered for searching would include other regulatory bodies that have Documents in place for protection of human health (e.g., Health Canada, the Australian Government's Therapeutic Goods Administration and the Food Documents agency, European Commission, etc.). The search finds that none of these sources list a risk value for Compound Alpha related to the potential for cancer with exposure to Compound Alpha.

The lack of identified risk values means that the scientific literature will need to be searched. The risk assessor designs a search strategy for a search of the publicly available scientific literature using the name "Compound Alpha"/the Chemical Abstracts Service (CAS) Number linked with terms such as "cancer" and "carcinogen" and "genotoxic". The risk assessor identifies both animal data and human data discussing the link of Compound Alpha to cancer and retrieves the full study reports for analysis of the data quality. Table E-1 below provides a summary of the type of studies and data that were identified.

[16] The term "Compound Alpha" is used in this appendix to represent the name of a real chemical.

TABLE E-1 Publicly Available on Compound Alpha Related to Potential Carcinogenicity of the Compound				
Study Species	**Study Type**	**Study Quality Factors**	**Key Design Characteristics**	**Statistical Analysis Performed?**
In Vitro Animal Cells	Ames assay (with and without S9) Rat micronucleus test	Peer-reviewed paper Performed under GLP	Used OECD guidelines for the tests Used a positive control compound (both assays) Positive in the Ames assay but only with S9 included (metabolic activation) Positive in the *in vitro* micronucleus assay	No
Rat	Two year feeding study	Peer-reviewed paper No mention of GLP Study performed in the 1980's Both male and female animals were included in the design with 8 rats per sex per dose group.	Designed with two dose groups and a control diet group No reporting of level of feed intake per day. No increased incidence of tumors of any type were reported.	Yes
Human	Retrospective case-control study	Peer-reviewed paper Worker population Cancer of all types (no focus on one form of cancer) Exposure to Compound Alpha was poorly defined, based solely on whether a worker had worked for more than 5 years in a plant that made Compound Alpha.	Reported no increase in risk of cancer (no specific cancer type was specified)	Yes

Step 3: Are the studies and/or data adequate for NSRL derivation?
The rat study included relevant data, looking at a large sampling of organ histopathology, in both male and female animals over two years, and reported no increased incidence of tumors as compared to the control group. The only evidence of genotoxicity was in an Ames assay with metabolic activation. Only one low quality human study was identified, and exposure groups were poorly defined, relying on length of time employed in a plant making Compound Alpha. The results in the human study were consistent with the data collected in rats, however (no increased risk of cancer reported). Due to the negative data in both animals and humans, but the low quality of the studies overall, the risk assessor concludes that the data are insufficient to derive a NSRL with any certainty, even in light of the positive genotoxicity data (two studies only available publicly). This decision also would apply to consideration of dermal exposure since no dermal exposure data in animals were available. Compound Alpha is expected to be poorly absorbed through the skin, however, because of the chemical nature of the compound and data on similar compounds.

Step 4: Derive the NSRL
None will be derived.

Step 5: Compare the NSRL to the level of anticipated exposure
Since a NSRL was not derived, no comparison is possible. Due to the poor quality of data, the label for Compound Alpha would not include a cancer hazard warning.

For additional examples, OEHHA publishes documents describing the derivation process for NSRLs for some of the listed chemicals. Hyperlinks to the documents are provided in the Proposition 65 chemical list[17]

[17] https://oehha.ca.gov/proposition-65/proposition-65-list

Derivation of a MADL

Step 1: Is Compound Alpha Listed in the Proposition 65 List?
The risk assessor searches the current Proposition 65 to see if Compound Alpha is listed by the State of California as a Reproductive/Developmental Toxicant (the Proposition 65 List) and finds Compound A is listed but no MADL has been derived by OEHHA.

Step 2: Do scientific studies and/or data exist that can be used to derive a MADL for Compound Alpha?
The risk assessor searches sites where regulatory authorities list risk values that have already been derived for Compound Alpha focusing on risk values linked to endpoints of reproductive and/or developmental toxicity. The sites to be searched would include those considered by OEHHA as authoritative bodies (*i.e.,* the U.S. Environmental Protection Agency (EPA), the World Health Organization's International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), the National Institute for Occupational Safety and Health (NIOSH), and the U.S. Food and Drug Administration (FDA). Other sites that should be considered for searching would include other regulatory bodies that have documents in place for protection of human health (*e.g.,* Health Canada, the Australian Government's Therapeutic Goods Administration and the Food Documents agency, European Commission, *etc.*). The search finds that none of these sources list a risk value for Compound Alpha related to reproductive and/or developmental toxicity.

The lack of identified risk values means that the scientific literature will need to be searched. The risk assessor designs a search strategy[18] for a search of the publicly available scientific literature using the name "Compound Alpha" linked with terms such as "reproduction" and "development" and "toxic". The risk assessor identifies both animal data and human data discussing the link of Compound Alpha to adverse effects on reproduction and retrieves the full study reports for analysis of the data quality. Table E-2 below provides a summary of the type of studies and data that were identified.

TABLE E-2
Publicly Available Studies on Compound Alpha Addressing Reproductive and/or Developmental Toxicity

Study Species	Study Type	Study Quality Factors	Key Design Characteristics	Statistical Analysis Performed?
Rat	Oral 28-day study (gavage dosing)	Peer-reviewed paper No mention of GLP (academic lab)	Control group included Multiple test doses (two and a control) One sex (adult male rats only) with 5 rats/	Yes

[18] It should be noted that this part of the process requires the risk manager to have some expertise in toxicology and should not be performed by someone without such expertise.

TABLE E-2 Publicly Available Studies on Compound Alpha Addressing Reproductive and/or Developmental Toxicity				
Study Species	**Study Type**	**Study Quality Factors**	**Key Design Characteristics**	**Statistical Analysis Performed?**
			group Examined male reproductive organs as part of the study A NOEL and a LOEL were established.	
Rat	Two year feeding study	Peer-reviewed paper No mention of GLP Study performed in the 1980's Both male and female animals were included in the design with 5 rats per sex per dose group.	Designed with two dose groups and a control diet group No reporting of level of feed intake per day. No increased incidence of tumors of any type were reported, including in the testes of other male reproductive organs.	Yes
Human	Retrospective observational cohort study	Peer-reviewed paper No mention of GCP (academic lab)	Worker study Control group included Endpoint of concern was effects on male and female reproductive capacity Several hundred workers in each of the cohort groups	Yes
Human	Case reports (five different papers)	Peer-reviewed papers	Male infertility endpoints (low testosterone levels; low sperm count)	No

Step 3: Are the studies and/or data adequate for MADL derivation?
Although no large GLP-compliant animal study is available, the rat study included relevant data and showed statistically significant differences with Compound Alpha exposure. The animal study data, damage to testes and reduced sperm numbers in males, was consistent with observations in human case reports and a human observational cohort study. The risk assessor concludes that the data are sufficient to derive a MADL for the oral route of exposure.

Step 4: Derive the MADL for Compound Alpha
The 28-day gavage study in rats can be used to derive the MADL as follows:

1. *Oral Rat NOEL for Compound Alpha is converted to a Human Equivalent NOEL in units of mg/kg-day using Body Weight (BW) scaling.*

2. *Oral Human Equivalent NOEL (mg/kg-day) is converted to µg/day by using the most appropriate BW based for humans (see Section 5.2.3)*

3. *Oral Human Equivalent NOEL (µg/day) ÷ 1000 = MADL (µg/day)*

As per OEHHA's Proposition 65 regulation, a 1000-fold factor was applied to the human equivalent NOEL.

Step 5: Compare the MADL to the level of anticipated exposure
The last step is to compare the MADL (µg/day) with anticipated levels of exposure through oral, dermal, and inhalation intake. The comparison is to determine if the MADL > or < the exposure value (see the flow diagram).

For additional examples, OEHHA publishes documents describing the derivation process for MADLs for some of the listed chemicals. Hyperlinks to the documents are provided in the Proposition 65 chemical list[19]

[19] https://oehha.ca.gov/proposition-65/proposition-65-list

International Association of Plumbing and Mechanical Officials (IAPMO)

4755 East Philadelphia Street | Ontario, California, 91761
1-800-854-2766 | 1-909-472-4100 |