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July 31, 2013

Via Electronic Mail

Ms. Monet Vela
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1001 I Street
Sacramento, CA 95812
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Re: Comments on Request for Public Participation and Notice of Public Workshops and Public Comments, Title 27, California Code of Regulations Proposed Section 25904 Listings by Reference to the California Labor Code

Dear Ms. Vela:

I am submitting these comments pursuant to OEHHA's request for public comments on the draft Labor Code regulations.

Introduction

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) issued a pre-proposal regulation for the stated purpose of implementing the Labor Code listing mechanism contained in Health and Safety Code section 25249.8(a) by proposing a new section 25904, Title 27, California Code of Regulations.

The U.S. Occupational Safety and Health Administration (OSHA) initially promulgated the Hazard Communication Standard (HCS) in 1983. Three years later, California adopted the Safe Drinking Water and Toxic Enforcement Act of 1986, Proposition 65. Proposition 65, in Health and Safety Code section 25249.8, provides that the Governor's list of chemicals known to the state to cause cancer or reproductive toxicity shall contain "those substances identified by reference in Labor Code Section 6382(b)(1) and . . . (d)." Those subdivisions provide as follows:

> **Section 6382(b)(1):** Substances listed as human or animal carcinogens by the International Agency for Research on Cancer (IARC).
>
> **Section 6382(d):** Notwithstanding Section 6381, in addition to those substances on the Director's list of hazardous substances, any substance within the scope of

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> the Federal Hazard Communication Standard (29 C.F.R. Sec. 1910.1200) is a hazardous substance subject to this chapter.

The reference in subdivision (b)(1) is IARC and the chemicals identified are those listed by IARC as human or animal carcinogens in its Monographs on the Evaluation of Carcinogenic Risks to Human. OEHHA incorrectly reads subdivision (d) to include two references: the Director's list of hazardous substances, and the federal HCS, 29 C.F.R. section 1910.1200. In fact, the subdivision properly construed is limited to only, the federal HCS.

Until 2012, the HCS mandated that employers treat substances as carcinogens if the substances were: (1) identified as carcinogens in an OSHA substance-specific standard, or (2) classified as a carcinogen or potential carcinogen by the IARC Monograph or the National Toxicology Program's (NTP) Report on Carcinogens (RoC). The 2012 amendments to the federal HCS (HCS 2012) align the HCS with three aspects of the United Nations' Globally Harmonized System of Classification and Labeling of Chemicals (GHS). HCS 2012 continues to mandate that employers automatically treat substances as carcinogens if they are so-identified in an OSHA substance-specific standard, but mandatory treatment as a carcinogen based on an IARC or RoC listing is no longer required.[1] Rather, HCS 2012 directs the domestic manufacturer or importer to self-classify each chemical based on a strength/weight of evidence analysis. OEHHA's draft regulation circumvents the changes mandated by HCS 2012.

OEHHA would exceed the scope of its authority if it were to adopt the regulation it drafted regarding the listing of chemicals pursuant to the Labor Code references contained in Proposition 65. Specifically, the draft regulation expands the scope of Proposition 65 and the Labor Code provisions, and is inconsistent with the Federal Hazard Communication Standard that is the principal basis of the Labor Code provision.

OEHHA's draft and June 17, 2013, Labor Code workshop discussions demonstrate that OEHHA views the Labor Code listing criteria to authorize the listing of a chemical on the basis of:

1. The California Director's list;
2. 29 C.F.R. part 1910.1200, subpart Z of OSHA's health standards;
3. Inclusion in the NTP RoC based on sufficient animal or human evidence; and
4. The subject of an IARC Monograph based on sufficient animal or human evidence.[2]

OEHHA is mistaken, and its draft approach not only ignores the overall structure of Proposition 65, but it also raises significant Constitutional issues of due process and unlawful delegation.

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[1] 77 Fed. Reg. 17,574 (March 26, 2012). OSHA refers to the superseded HCS as "HCS 1994" and the current standard as "HCS 2012." The 2012 amendments aligned the HCS with Revision 3 of the United Nations' Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

[2] PROPOSED HEALTH & SAFETY CODE SECTION 25904 and *Regulatory concept for Section 25904, Title 27, California Code of Regulations: Chemical Listings by Reference to the California Labor Code,* Pre-Regulatory Workshop, OEHHA (June 17, 2013), slide 5.

- The Director's list is not a basis for listing a chemical under Proposition 65. The opening clause of section 6382(d), which states, "Notwithstanding Section 6381, in addition to those substances on the director's list of hazardous substances," is irrelevant for purposes of the Labor Code listing mechanism, and never before have the courts interpreted the provision as giving OEHHA authority to refer to the Director's list when updating and amending the Proposition 65 list.[3] The scope and relevance of section 6382(d) has always been limited to chemicals within the scope of the federal HCS.[4] Construing subdivision (d) as including the Director's list as a reference ignores the context of that subdivision.

- OEHHA's failure to analyze properly the HCS 2012 is reflected in its proposal that the Proposition 65 list can include a chemical identified as causing cancer or reproductive or developmental toxicity in 29 C.F.R. part 1910.1200, subpart Z. Appendix A.6 of 29 C.F.R., part 1910.1200 addresses the classification of carcinogens, and Appendix A.7 addresses the classification of reproductive toxicants. While Appendix A.6 requires businesses to classify a chemical as a carcinogen when OSHA has included cancer as a health hazard in subpart Z, Appendix A.7 contains no such provision for reproductive toxicants. Accordingly, OEHHA has no basis for proposing a regulation that would authorize it to add to the Proposition 65 list as a reproductive or developmental toxicant, a chemical listed in subpart Z.

- The NTP/IARC feature of the listing "process" described by OEHHA is nothing more than a declaration that any finding by NTP or IARC of human carcinogenicity or reproductive toxicity renders that chemical a Proposition 65 chemical. To reach this conclusion, OEHHA distorts the language of the HCS 2012 and ignores express and contemporaneous interpretation by OSHA as to the meaning and scope of those provisions. The requirement under HCS 1994 to treat NTP's RoC and IARC's Monographs as establishing that a chemical is a carcinogen was repealed under HCS 2012. In its place, manufacturers and importers are directed to evaluate their chemicals in accordance with section 1910.1200 and determine the hazard class or classes using a weight of evidence approach and consulting Appendix A for classification of health hazards.

Additionally, OEHHA's statements that the hazard assessment made by any one employer or manufacturer and disclosed on a SDS is sufficient to draw that chemical within the HCS, violate the fundamental principles of due process. Under that approach, there would be no mechanism for challenging the propriety of an arbitrary, capricious, or otherwise improper employer or manufacturer's SDS classification. Beyond this fatal flaw, a system in which a hazard classification by any one company would effectively bind all other companies borders on government-enforced anarchy. Because OEHHA would be empowering any one company to oblige all others, it would clearly be an unlawful delegation of authority.

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[3] *See e.g., SIRC v. OEHHA*, Cal.App.3rd No. C0643d (2012); *California Chamber of Commerce v. Brown*, 196 Cal.App.4th 233 (2011); and *AFL-CIO v. Deukmejian*, 212 Cal.App.3d 425 (1989).
[4] *Id.*

The HCS 1994 provisions that created a referenced floor of chemicals deemed to be hazardous or deemed to be carcinogens have been eliminated except for substances designated as carcinogens by OSHA.[5] The effect of the draft regulation is to ignore those critical changes to the HCS and proceed as if HCS 1994 remained in place by holding on to the outdated concept that any finding of carcinogenicity under an IARC Monograph or the NTP RoC is sufficient for a chemical to be within the scope of the federal HCS.

Through the evolution of workplace safety and health best practices, the world consensus is that all health hazard classifications, including carcinogenicity and reproductive toxicity, must be based on weight of evidence (WOE), and IARC and NTP findings, which are not based on WOE, do not merit a presumption of validity. OSHA no longer treats the finding of IARC and NTP as conclusive under the HCS 2012 and makes reliance on them an individual option for each manufacturer or importer. Thus, given that OSHA no longer deems the IARC and NTP findings to be binding, they no longer fall within Labor Code section 6382(d), and OEHHA cannot expand the scope of the statute to include chemicals that are outside its scope (even if they were previously within its scope). Furthermore, OSHA expressly sought in HCS 2012 to create a uniformity standard for the presentation of hazard information. California cannot adopt or maintain a mechanism that results in conflicting classifications, labels and SDS for chemicals. OEHHA's proposed rule would do just that. The unacceptable consequence would be that employees receive conflicting messages about the chemical would undermine the effectiveness and credibility of the hazard communication system. Federal preemption would apply to prevent the conflicting California rule from making it impossible to achieve the goals of the HCS.

When OEHHA decides to proceed with a regulation to articulate the criteria it will follow in listing chemicals pursuant to the Labor Code references, it must do so consistently with the provisions of Proposition 65, the Labor Code, the federal HCS, and with the holdings of the courts in *AFL-CIO v. Deukmejian,* 212 Cal.App.3d 425 (1989), *Western Crop Protection Ass'n v. Davis*, 80. Cal.App.4th 741 (2000), and *SIRC v. OEHHA,* Cal.App.3rd No. C0643d (2012). Accordingly, the references and chemicals that may be considered for listing are as follows:

1. Substances listed as human or animal carcinogens by IARC. This is the specific and only reference contained in section 6382 (b)(1).
2. Chemicals for which OSHA has included cancer as a health hazard in subpart Z. This is the only provision in the federal HCS that designates specific substances as hazardous chemicals and specifies their classification, *i.e.*, a carcinogen.

The following references and chemicals are not valid for inclusion:

1. The Director's list. Section 6382(d) added the reference to the federal HCS. The Director's list was established by section 6380. Hence, when section 6382(d) is read in context, the only reference is the HCS.
2. NTP's Annual Report on Carcinogens and IARC Monographs, except as provided in subdivision (b)(1). Subdivision (d) refers to the federal HCS. OSHA, in amending the

[5] See 29 C.F.R. part 1910, subpart 3.

HCS in 2012, made clear in its Federal Register statements that it fully intended to remove any list of chemicals that are to be treated as hazardous. The purpose of subdivision (d) is to conform California law to the federal HCS. Accordingly, subdivision (d)'s reference to the HCS no longer incorporates the chemicals listed by NTP or IARC.

3. Any chemical causing reproductive toxicity. Subdivision (b)(1), limited to IARC carcinogens, obviously is not a reference to any list of chemicals causing reproductive toxicity. Subdivision (d)'s reference to the federal HCS leads to no list of chemicals that causes reproductive toxicity. Appendix A to the HCS specifically states that chemicals listed in subpart Z are to be classified as carcinogens because OSHA determined that they cause cancer in a rulemaking. Appendix A contains no similar provision with respect to reproductive toxicants.

Finally, the three above-cited cases make clear that OEHHA may list only those chemicals for which the authoritative body compiling the list based its listing decision on sufficient evidence demonstrating that the chemical causes cancer or reproductive toxicity. Accordingly, OEHHA should include provisions in its regulation describing the process that it will follow in determining whether IARC or OSHA based its decision on sufficient evidence of causation in compiling respectively its list of human or animal carcinogens or carcinogens under C.F.R. part 1910, subpart Z.

I. Labor Code Section 6382 Does Not Authorize Listing based on the "Director's List"

OEHHA's authority is constrained by the language of Proposition 65 and the Labor Code provisions. Proposition 65 limits the chemicals to be listed by the Labor Code Mechanism to "substances identified by reference" in the Labor Code. At most, Proposition 65 permits OEHHA to add to the Proposition 65 list only those known carcinogens and reproductive toxins that are identified as hazards in the references contained in the two Labor Code subdivisions. Hence, the inquiry turns to the Labor Code to determine the relevant references and the chemicals identified as hazards in those references.

Health and Safety Code section 25249.8 (a) reads:

> On or before March 1, 1987, the Governor shall cause to be published a list of those chemicals known to the state to cause cancer or reproductive toxicity within the meaning of this chapter, and he shall cause such list to be revised and republished in light of additional knowledge at least once per year thereafter. Such list shall include at a minimum those substances identified by reference in Labor Code Section 6382(b)(1) and those substances identified additionally by reference in Labor Code Section 6382(d).

Labor Code section 6382 is part of Division 5, Safety and Employment, Chapter 2.5, Hazardous Substances Information and Training, Article 3, Hazardous Substances, and a simple, sequential reading of the referenced Labor Code provisions is highly instructive.

Section 6380 requires the Director of the Department of Industrial Relations to establish a "list of hazardous substances" pursuant to section 6282.

Section 6381 provides that any substance not on the list shall not be subject to the provisions of Chapter 2.5, Hazardous Substances Information and Training, but it also ensures that employers do not avoid other obligations to provide safe workplaces because a substance does not appear on the Director's List.

Section 6382 is a scoping section. It presents the criteria upon which the Director will base the list of hazardous substances, a list that defines the universe of substances subject to this part of the Labor Code. The pertinent portions of section 6382 referenced by Proposition are:

> The director shall prepare and amend the list of hazardous substances according to the following procedure:
>
> . . .
>
> (b) The listings referred to in subdivision (a) are as follows:
>
> (1) Substances listed as human or animal carcinogens by the International Agency for Research on Cancer (IARC).
>
> . . .
>
> (d) Notwithstanding Section 6381, in addition to those substances on the director's list of hazardous substances, any substance within the scope of the federal Hazard Communication Standard (29 C.F.R. Sec. 1910.1200) is a hazardous substance subject to this chapter.

Subdivision (b)(1) is relatively simple and straightforward. The reference is IARC and the chemicals identified are those listed by IARC as human or animal carcinogens. Subdivision (d), however, is more complicated, and OEHHA mistakenly reads subdivision (d) to include two references: the Director's list of hazardous substances, and the Federal Hazard Communication Standard, 29 C.F.R. section 1910.1200. In fact, the subdivision properly construed is limited to only one reference, the HCS.

Section 6382(d) can only be reasonably understood by considering the referenced section 6381 within the context of the Director's list. In simple terms, 6382(d) says that even if substances are not on the Director's list, substances are still subject to the Labor Code provisions if the substance falls within the scope of the federal Hazard Communication Standard.

Further supporting the conclusion that OEHHA has misapplied the language of section 6382(d) is that under the agency's reading of subdivision (d), a redundancy is created. As applied by

OEHHA, substances on the Director's List would be subject to the Chapter by virtue of section 6380 as well as section 6390 of the Labor Code. As noted, section 6380 requires the Director to establish a list of hazardous substances, and section 6390 requires manufacturers of substances on the list to prepare material safety data sheets. Hence, subdivision (d) is not needed to make the Director's list subject to the Chapter; it is needed only to make substances within the HCS subject to the chapter. The redundancy is avoided by reading subdivision (d) in context with the Article, commencing with section 6380, and certainly when read in context with the Chapter, commencing with section 6360. Accordingly, the provision in Proposition 65 that requires the Governor's list to include chemicals identified by reference in Labor Code section 6382(d) refers only to the federal HCS and not to the Director's list. This interpretation is supported by the courts and the Ballot Argument in favor of Proposition 65.

In *AFL-CIO v. Deukmejian*, 212 Cal. App. 3d 425 (1989), the Court explained that Labor Code section 6382, subdivision (d), refers to '... any substance within the scope of the federal Hazard Communication Standard (HCS) (29 C.F.R. Sec. 1910.1200). . . .' [Omission of first part of sentence is the Court's].[6] It did not mention the Director's list as a source in section 6382(d), and it left out the phrase "in addition to those substances on the director's list of hazardous substances" in its discussion. The Court also found that the initial Proposition 65 list, which was created by reference to Labor Code sections (b)(1) and (d), contained substances from the IARC's list, the NTP's list and OSHA's list.[7] There is no mention of substances from the Director's list. Similarly, the Courts of Appeal in *California Chamber of Commerce v. Brown,* 196 Cal.App.4th 233 (2011), and *SIRC v. OEHHA*, 210 Cal. App. 4th 1082 (2012), did not cite the Director's list to be an authorized Proposition 65 listing source.

The Ballot Argument states, "At a minimum, the Governor must include the chemicals already listed as known carcinogens by two organizations of the most highly-regarded national and international scientists: the U.S.' National Toxicology Program, and the U.N.'s International Agency for Research on Cancer." The obvious reference is to the Proposition 65 provision requiring the Governor to include, "[a]t a minimum, those substances identified by reference in Labor Code section 6382(b)(1) and . . . (d)." No other provision includes the concept of "at a minimum," and no other provision implicates NTP or IARC. Further, no reference is made in the Ballot Argument to the Director's list.

From a Proposition 65 perspective, substances that are known carcinogens and fall within the scope of the federal Hazard Communication Standard may be listed. However, section 6382(d) does not provide OEHHA the authority to list substances under Proposition 65 merely because those chemicals have been listed by the Director of Industrial Relations as hazardous substances. In fact, OEHHA, in the draft regulation, is (1) expanding its statutory authority and (2) adopting a new interpretation, because under its proposal OEHHA would be allowed to list from each of the sources listed in section 6382(b)(1)-(5) since the substances on the Director's list are derived from each of those sources.

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[6] *AFL-CIO v. Deukmejian*, 212 Cal. App. 3d at 433-35, 437 (1989).

[7] *Deukmejian*, 212 Cal. App. 3d at 430.

As explained by the court in *Brown*:

- Labor Code section 6382 is part of the Hazardous Substances Information and Training Act (HSITA) (Lab. Code, § 6360 et seq.) and sets forth criteria for the preparation and amendment of a list of 'hazardous substances' in the workplace (*Id.*, § 6380), known as the 'HSITA list.' (*Id.*, § 6380.)[8]
- This Director's list, as it is commonly known, is a compilation of hazardous chemicals for the workplace that have been identified pursuant to section 6382(b) as:
  - carcinogens by IARC (§ 6382(b)(1));
  - federal Clean Water Act toxic pollutants, oil or hazardous substances as determined by the U.S. Environmental Protection Agency (§6382(b)(2));
  - federal Clean Air Act hazardous air pollutants as determined by the EPA (§6382(b)(2));
  - airborne chemical contaminants by the Occupational Safety and Health Standards Board (§6382(b)(3)); and
  - restricted materials with known, adverse human health effects by the Director of Food and Agriculture (§6382(b)(4)).
- Substances for which an information alert has been issued by the repository of current data also can be listed.[9]

OEHHA's proposed regulatory implementation of the Labor Code is flawed based on a failure to read paragraph (d) of section 6382 in context of the entire Labor Code chapter. When this is done, there is no support for OEHHA's proposal that a Proposition 65 listing can be initiated for a chemical that is on the Director's list. The opening clause of section 6382(d), which states, "Notwithstanding Section 6381, in addition to those substances on the Director's List of hazardous substances," is meaningless <u>for purposes of the Labor Code listing mechanism</u>. The scope and relevance of section 6382(d) for purposes of implementing the Labor Code listing mechanism is limited to chemicals within the scope of the federal HCS that are known to be carcinogens.[10]

II. OEHHA Distorts "Within the Scope" of the Federal HCS

The California HSITA was initially adopted in 1980. Section 6382 contained only subdivisions (a), (b), and (c) at that time. In 1983, OSHA adopted the HCS, 29 C.F.R. section 1910.1200. To ensure that California law was at least as effective as the federal law, the Department of Industrial Relations (DIR) proposed a bill to amend section 6382 that, among other things, conformed California's HSITA with the federal HCS. Documents constituting the legislative history on the conformity bill, AB 1042 (1985), are replete with statements confirming the purpose of what is subdivision (d) today.

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[8] *California Chamber of Commerce v. Brown*, 196 Cal.App.4th 233, 240.
[9] LABOR CODE section 6382.
[10] *See e.g., SIRC v. OEHHA*, Cal.App.3rd No. C0643d (2012); *California Chamber of Commerce v. Brown*, 196 Cal.App.4th 233 (2011); and *AFL-CIO v. Deukmejian*, 212 Cal.App.3d 425 (1989).

DIR's Enrolled Bill Reports (EBR) states that it sponsored the bill to make HSITA as inclusive as the federal HCS by providing "that substances within the scope of the federal Hazard Communication Standard (HCS) be subject to the provisions of HSITA." The Department of Finance, in its EBR, states, "This bill would amend State law to bring it into conformity with the Federal Hazard Communication Standard." It would do so by providing that, "Any substance within the scope of the Federal Hazard Communication Standard is a hazardous substance subject to the Hazardous Substance Information and Training Act." The author, Assemblyman Bill Jones, in his letter urging Governor Deukmejian to sign AB 1042, confirmed that the purpose of AB 1042 was to conform state law to the federal HCS. The same statements are found throughout the bill analysis prepared by legislative committees and state agencies.

Every indication is that the Legislature intended that subdivision (d) of section 6382 conform California law to the federal HCS. Nothing in that subdivision can be construed to imply that the reference includes substances other than those covered by the federal HCS. Hence, when OSHA deletes from the hazard classification requirements the established lists of chemicals that are deemed hazardous chemicals, or are deemed carcinogens under the HCS in all situations, those lists are deleted from the state HSITA program as well. To construe subdivision (d) to still refer to the NTP's Annual Report and IARC's Monographs, despite the fact that when OSHA explicitly amended the HCS in 2012 to delete the mandatory classifications based on those documents, is to ignore both the purpose of subdivision (d) and the effect of OSHA deleting those references as hazardous substances. Subdivision (d) has to be read to conform state law to the federal law. OEHHA cannot ignore OSHA's explanation that it has removed the NTP and IARC list as chemicals that are to be considered carcinogens and hazardous chemicals.

Having established that the federal HCS is the only relevant reference in subdivision (d), the inquiry turns to what are the chemicals identified by reference in the HCS. Pursuant to Labor Code section 6382(d), a chemical cannot be listed on the Proposition 65 List of Chemicals unless the chemical is "within the scope of the Federal hazard communication standard". For a chemical to be "within the scope of the HCS" for purposes of Prop 65, the following fundamental conditions must exist:[11]

(1) the substance is deemed a carcinogen or reproductive toxicant by the federal HCS; and
(2) evidence of carcinogenicity and reproductive toxicology rises to the "known" level.[12]

OEHHA states that "the proposed regulation describes ***the process*** by which OEHHA identifies chemicals or substances that are 'within the scope' of the federal Hazard Communication Standard and are identified as human or animal carcinogens or reproductive toxicants, and therefore must be included on the list by reference to Labor Code section 6382(d)."[13] Yet, the listing "process" described by OEHHA is nothing more than a declaration that any finding by

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[11] *Initial Statement of Reasons*, Title 27, California Code of Regulations, Proposed section 25904, Listing by Reference to the California Labor Code at 9, available at http://oehha.ca.gov/prop65/CRNR_notices/pdf_zip/051713DRAFT_ISOR_LCreg.pdf (last accessed May 31, 2013).
[12] *SIRC v. OEHHA*, Cal.App.3rd No. C0643d (2012).
[13] *See* Initial Statement of Reasons at 5 (emphasis added).

NTP or IARC of human carcinogenicity or reproductive toxicology renders that chemical a Proposition 65 chemical. OEHHA is not permitted to expand the scope of the authority granted to it by the legislature by creating a new listing mechanism. As OEHHA well knows, the regulatory text of HCS 2012 and the preamble to the Final Rule clearly reject that outdated approach to hazard communication.[14] OEHHA disregards its limited statutory authority and the 2012 amendments to the HCS and proposes regulatory text and provides explanations in its *Initial Statement of Reasons* that clearly reflect an inappropriate analysis.

A. Under HCS 2012 Appendix A is Used to Identify Health Hazards

Under HCS 2012, importers and manufacturers must identify the class and category of all health hazards presented by a chemical covered by the HCS and enter that information in Section 2 of the SDS. As the rule makes clear, the sole source to be used in identifying those health hazards is Appendix A of HCS 2012. Relevant portions from the OSHA Side-by-Side Comparison are in Attachment A to these comments.

First, the definition of the term "health hazard" in section 1910.1200(c) states:

> "Health hazard" means a chemical which is classified as posing one of the following hazardous effects: acute toxicity (any route of exposure); skin corrosion or irritation; serious eye damage or eye irritation; respiratory or skin sensitization; germ cell mutagenicity; **carcinogenicity**; reproductive toxicity; specific target organ toxicity (single or repeated exposure); or aspiration hazard. ***The criteria for determining whether a chemical is classified as a health hazard are detailed in Appendix A to §1910.1200 -- Health Hazard Criteria*** (emphasis added).

Second, section 1910.1200(d)(2) provides:

> (d)(2) Chemical manufacturers, importers, or employers classifying chemicals shall identify and consider the full range of available scientific literature and other evidence concerning the potential hazards. There is no requirement to test the chemical to determine how to classify its hazards. ***Appendix A to §1910.1200 shall be consulted for classification of health hazards,*** and Appendix B to §1910.1200 shall be consulted for the classification of physical hazards (emphasis added).

[14] *See SIRC v. OEHHA* (2012); and "Proposition 65, The Labor Code Listing Mechanism, and the OSHA Hazard Communication Standard."

B. Carcinogens

1. OSHA HCS 2012 Directs Classifiers to Use a Weight of the Evidence Evaluation

Prior to 2012, 29 C.F.R. section 1910.1200 (d)(4) of the federal HCS required manufacturers, importers, and employers to treat three sources as establishing that a chemical is a carcinogen. These sources were NTP's Annual Report on Carcinogens, IARC's Monographs, and the chemicals determined by OSHA to be carcinogens through substance-specific rulemakings and listed in 29 C.F.R. part 1910, subpart Z. This is no longer the case; yet the effect of OEHHA's draft regulation is to apply the old HCS standard (HCS 1994) instead of the HCS as amended in 2012. Under HCS 2012, all requirements based on the NTP RoC and IARC Monographs have been eliminated. Instead, manufacturers and importers are required to self- "identify and consider the full range of available scientific literature and other evidence concerning the potential hazards",[15] and then apply the applicable classification criteria in Appendix A to 29 C.F.R. section 1910.1200 under a weight of evidence analysis.[16]

In other words, under HCS 2012, there is no referenced floor of chemicals deemed to be hazardous chemicals or deemed to pose a particular hazard. Instead, Appendix A provides specific, detailed criteria for each type of health hazard to guide the evaluation of relevant data and subsequent classification of the chemical. Reliance on the detailed and comprehensive classification criteria developed through the GHS international collaborative process means that, except for chemicals identified as potential carcinogens by OSHA through a substance-specific rulemaking, there no longer is a requirement to rely on a cancer determination or any type of chemical hazard determination produced by a governmental agency (such as NTP or IARC) or a non-governmental organization (such as a chemical manufacturer). OSHA explained the basis for the amendment as follows:

> With the detailed criteria, and the weight of evidence approach in the GHS, OSHA indicated in the NPRM that it appeared to no longer be necessary to have such a floor or the one study rule.

As noted by OEHHA, while Appendix A to 29 CFR section 1910.1200 "***allows*** a manufacturer or employer to rely on the NTP designations for purposes of classifying chemicals,"[17] it is not mandatory and not determinative. In this regard, OSHA, under the 2012 HCS amendments, departed from HCS 1994 and now states that you "*may* [as opposed to "shall"] treat the following sources as *establishing* that a chemical is a carcinogen or potential carcinogen for hazard communication purposes". [18]

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[15] 29 C.F.R. section 1910.1200(d)(2). Like the HCS, the GHS approach is based on a downstream flow of information from suppliers to users; self-classification ..... 77 Fed. Reg. at 17,707.
[16] 29 C.F.R. section 1910.1200, A.0.3 (Classification based on Weight of Evidence).
[17] *Initial Statement of Reasons* at 9 (emphasis added).
[18] 29 C.F.R. section 1910.1200, A.6.4.1 (emphasis added).

From a Proposition 65 listing perspective, there is a critical statutory distinction between manufacturers being *required* to treat a substance as a carcinogen or having the *option* to treat a substance as a carcinogen. Classification of a chemical as a carcinogen for OSHA purposes must be based on weight of evidence considerations under section A.6.2.1 of 29 C.F.R. section 1910.1200. The nature of this inquiry is succinctly stated in the *Carcinogen Classification* (section A.6.2.3):

> Carcinogen classification is a one-step, criterion-based process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.[19]

OSHA's decision to employ an integrated weight of evidence approach is consistent with recognized and accepted scientific principles.

The criteria for determining whether a chemical is classified as a health hazard are detailed in mandatory Appendix A to section1910.1200, *Health Hazard Criteria*.[20] A review of the completely overhauled Appendix A demonstrates that the HCS now operates under a weight of evidence framework, and NTP and IARC determinations are no longer treated as conclusive findings of carcinogenicity under the HCS. The current Appendix A is added to these comments as Attachment B.

2. OSHA's List of Carcinogens

As noted above, the only chemicals that are deemed carcinogens under HCS 2012, such that a self-implemented assessment need not be completed, are those chemicals identified as potential carcinogens by OSHA through a substance-specific rulemaking. Section A.6.4.2 of 29 C.F.R. section 1910.1200 states:

> Where OSHA has included cancer as a health hazard to be considered by classifiers for a chemical covered by 29 CFR part 1910, Subpart Z, Toxic and Hazardous Substances, chemical manufacturers, importers, and employers shall classify the chemical as a carcinogen.

The list of toxic and hazardous substances under subpart Z of part 1910 of the OSHA regulations is quite limited and consists of only the following:

1910 Subpart Z - Toxic and Hazardous Substances

> 1910.1001 - Asbestos.
> 1910.1004 - alpha-Naphthylamine.
> 1910.1006 - Methyl chloromethyl ether.

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[19] *Id.* at 17,807.
[20] *See*, Side-by-Side at 9.

1910.1007 - 3,'-Dichlorobenzidine (and its salts).
1910.1008 - bis-Chloromethyl ether.
1910.1009 - beta-Naphthylamine.
1910.1010 - Benzidine.
1910.1011 - 4-Aminodiphenyl.
1910.1012 - Ethyleneimine.
1910.1013 - beta-Propiolactone.
1910.1014 - 2-Acetylaminofluorene.
1910.1015 - 4-Dimethylaminoazobenzene.
1910.1016 - N-Nitrosodimethylamine.
1910.1017 - Vinyl chloride.
1910.1018 – Inorganic arsenic
1910.1025 - Lead.
1910.1027 - Cadmium
1910.1028 - Benzene.
1910.1029 - Coke oven emissions.
1910.1044 - 1,2-dibromo-3-chloropropane.
1910.1045 - Acrylonitrile.
1910.1047 - Ethylene oxide.
1910.1048 - Formaldehyde.
1910.1050 - Methylenedianiline
1910.1051 - 1,3-Butadiene.
1910.1052 - Methylene Chloride.

Accordingly, OEHHA can reference subpart Z for purposes of listing a chemical as a Proposition 65 carcinogen, but as discussed below, this is not true for reproductive toxicants.

3. *Informational References to NTP and IARC on SDSs Do Not Constitute a Finding that a Chemical is a Known Carcinogen Within the Scope of the Federal HCS*

There is no legal basis for the proposed provision that the HCS requirement to reference an NTP or IARC finding on an SDS triggers the Proposition 65 listing mechanism. In addition to creating an unworkable regime, OEHHA completely ignores OSHA's explicit statement that the requirement to list NTP and IARC classifications on SDSs is merely informational and not reflective of hazard classification.[21]

The purpose of Appendix D of HCS 2012 is to establish a uniform format and content for SDSs once the classification has been determined. The intent is to create consistency and promote a more worker-friendly, harmonized format. Appendix D does not control how a hazardous chemical is classified by importers or manufacturers. In fact, when discussing the requirement to include NTP and IARC classifications in the Toxicological Information section of the SDS,

[21] 77 Fed. Reg. at 17,735.

OSHA repeatedly stated that the requirement was merely informational and not a determination of carcinogenicity under the HCS.[22]

OEHHA, however, need not simply rely on inference to understand that both the NTP and IARC references in Appendix D are solely informational. OSHA stated this directly when describing the requirement to reference NTP and IARC on SDSs:

> In the NPRM, OSHA did not propose to continue to require specific mention of IARC, NTP, and OSHA as sources of determinations regarding carcinogenicity. The requirement to consider these sources definitive in terms of a carcinogen determination was not included in the NPRM since it was not part of the GHS approach. However, as was discussed above, OSHA has modified [Appendix A] and Appendix F to allow classifiers to use these [NTP and IARC] sources when assessing carcinogenicity, rather than applying the criteria to the data themselves. In order to facilitate this, OSHA has provided a table in Appendix F that aligns the GHS criteria with those of IARC and NTP. In addition, OSHA has decided to retain the requirement to include this information on the SDS in Section 11. This information will be of use to classifiers, as well as to employers and employees, when ascertaining potential hazards and determining appropriate control measures.[23]

In contrast, OSHA amended Appendix A to mandate that classifiers follow the cancer determinations made by OSHA in substance-specific rulemakings.[24] Thus, it is more than evident that the requirement in HCS 2012 to list NTP and IARC classifications on SDS does not make those substances carcinogens under the HCS. That determination remains the province of the employers or manufactures who make hazard determinations by applying the HCS 2012 criteria.

4. *Appendix F Does Not Mandate the Classification of Hazards*

Under HCS 2012, NTP's RoC and IARC's Monographs do not dictate a classification. NTP and IARC are specifically discussed under Appendix F to section 1910.1200, a non-mandatory section of the rule, which is titled Guidance for Hazard Classification Re: Carcinogenicity (Non-Mandatory). In describing Appendix F, OSHA states:

> The mandatory criteria for classification of a chemical for carcinogenicity under HCS (§ 1910.1200) are found in Appendix A.6 to this section. This non-mandatory Appendix provides additional guidance on hazard classification for carcinogenicity. Part A of Appendix F includes background guidance provided by GHS based on the Preamble of the International Agency for Research on Cancer (IARC) "Monographs on the Evaluation of Carcinogenic Risks to Humans"

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[22] 77 Fed. Reg. 17,574.
[23] *Id.* at 17,735.
[24] *See* 29 C.F.R. section 1910.1200, A. 6.4.2.

> (2006). Part B provides IARC classification information. Part C provides background guidance from the National Toxicology Program (NTP) "Report on Carcinogens" (RoC), and Part D is a table that compares GHS carcinogen hazard categories to carcinogen classifications under IARC and NTP, allowing classifiers to be able to use information from IARC and NTP RoC carcinogen classifications to complete their classifications under the GHS, and thus the HCS.[25]

In other words, if a manufacturer or importer *voluntarily* decides that it wants to rely on the NTP or IARC determination, it is permitted to do so, but this does not dictate an OSHA classification. Furthermore, as a non-mandatory section of HCS 2012, Appendix F does not provide a statutory basis for listing under the Labor Code Mechanism.

C. Reproductive Toxicity

1. *HCS 2012 Directs Classifiers to Use a Weight of the Evidence Evaluation*

The basis for classifying a chemical as a reproductive toxicant also is a weight of evidence evaluation plus the use of expert judgment.[26] Like carcinogens, the applicable classification criteria for reproductive toxicants is found in Appendix A of 29 C.F.R. section 1910.1200. Section A.7.2.3 specifically addresses reproductive toxicity and states:

> [Weight of evidence using expert judgment] means that all available information that bears on the determination of reproductive toxicity is considered together. Included is information such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs.
>
> The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, level of statistical significance for intergroup differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are considered together in a weight of evidence determination.

In other words, there is no reference list of reproductive toxicants, and classifiers must apply the detailed classification criteria laid out by OSHA in Appendix A, which requires a weight of evidence evaluation.

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[25] *Id.* at 17,885 (col. 1).
[26] 29 C.F.R. §§ 1910.1200, A.7.2.2 and A.7.2.3.

2. *Nothing in the Federal HCS Identifies Reproductive Toxicants*

In contrast to the cancer classification procedures, OSHA does provide that "a single, positive study performed according to good scientific principles and with statistically or biologically significant positive results *may* justify classification (See also A.7.2.2.3)."[27] However, reliance on a single study is tempered with the following requirements for establishing that a chemical is a *known* human reproductive toxicant under Section A.7.2.2.3 of 29 C.F.R. section 1910.1200:

> For human evidence to provide the primary basis for a Category 1A classification [known or presumed human reproductive toxicant] there must be reliable evidence of an adverse effect on reproduction in humans. Evidence used for classification shall be from well conducted epidemiological studies, if available, which include the use of appropriate controls, balanced assessment, and due consideration of bias or confounding factors. Less rigorous data from studies in humans may be sufficient for a Category 1A classification if supplemented with adequate data from studies in experimental animals . . . .

Furthermore, contrary to OEHHA's proposed interpretation of HCS 2012 and its coverage of all chemicals listed under 29 C.F.R. part 1910.1200, the OSHA HCS does not reference subpart Z chemicals as reproductive or development toxins under the HCS, This, in turn, means that there is no basis for a Labor Code reference listing of OSHA reproductive or developmental toxicants. Yes, OSHA has identified certain substances as reproductive toxicants, and, should OEHHA wish to proceed, other listing mechanisms would be an appropriate route, not the Labor Code listing mechanism.

III. The Individual Evaluation of a Manufacturer or Employer Cannot be the Basis for Finding that a Chemical is a Carcinogen or Reproductive Toxicant

Contrary to the views expressed by OEHHA, how an individual manufacturer or employer classifies a chemical under HCS 2012 is not relevant and cannot be the basis for a chemical classification under the Labor Code Mechanism. Fundamentally, a manufacturer's SDS classification does not demonstrate known carcinogenic or reproductive toxicity status. Consider that HCS 2012 states that when the WOE for carcinogenicity of a substance does not meet the Appendix A criteria, any positive study that reports statistically significant findings must be noted on the SDS.[28] The SDS, however, is not required to detail the basis for the manufacturer's classification and certainly not whether the single positive study supports a known finding of carcinogenicity or reproductive toxicity.

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[27] 29 C.F.R. Section A.7.2.3 (emphasis added).
[28] *See* 77 Fed. Reg. at 17, 807.

There also is a legitimate concern that this "process" could lead to abuse and manipulation of the marketplace. Consider the repercussions if the following statement by OEHHA was in fact true:

> when a chemical is classified by a manufacturer or employer as a carcinogen or a developmental or reproductive toxin pursuant to the above mandatory criteria, the chemical is, by definition, within the scope of the Hazard Communication Standard and will be listed under Proposition 65.[29]

Scenario 1

Foreign Company Y manufactures an alternative resin to styrene-based resins. Company Y seeks to establish a market in the U.S. Company Y produces a small amount of styrene-based reins to qualify it as a manufacturer of styrene-based products. Company Y classifies the styrene-based product as a carcinogen on its label and SDS to bring it within the scope of the HCS and Prop 65. Customers seek alternatives. Company Y facilitated an advantage.

Scenario 2

Company X manufactures a chemical product that competes with styrene-based products. Company X imports 1 shipment of styrene to the U.S. such that it becomes the importer of record. Company X classifies the styrene-based product as a carcinogen on its label and SDS to bring it within the scope of the HCS and Prop 65. Styrene-based products are harmed by the hazard warnings and the competitor sells its competing primary product line.

The fundamental point is that the language of the Labor Code listing mechanism and HCS 2012 does not provide a basis for viewing any manufacturer, importer or employer SDS classification as controlling for purposes of listing. The scenarios presented here address the mischief and policy errors that would derive from OEHHA letting any single SDS classification set the basis for listing under Proposition 65.

IV. *SIRC v. OEHHA* Limits Listing Chemicals for Which Sufficient Evidence Exists to Demonstrate that the Chemicals are Known to Cause Cancer or Reproductive Toxicity.

During the June 17, 2013, workshop, OEHHA raised the question whether the *SIRC v. OEHHA* decision should be construed to require sufficient evidence of carcinogenicity in humans or animals only for IARC 2B chemicals. OEHHA's question implies that it might rely on limited or inadequate evidence to add chemicals to the Proposition 65 list if some authoritative body other than IARC listed them. Under the draft regulation, those authoritative bodies would include the Director's list, NTP's Annual Report on Carcinogens, and 29 C.F.R. part 1910, subpart Z.

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[29] *Initial Statement of Reasons* at 8.

Any regulatory provision or action taken to list a chemical with less than sufficient evidence would be inconsistent not only with the *SIRC* decision, but also with the decision in *AFL-CIO v. Deukmejian*, 212 Cal. App. 3d 425 (1989), and *Western Crop Protection Ass'n v. Davis*, 80 Cal. App. 4th 741 (2000). Both of those cases are discussed and cited with approval by the *SIRC* Court.

At the outset, the *SIRC* Court states:

> Thus, the reference to Labor Code § 6382 and Health and Safety Code § 25249.8, subdivision (a), must be read in conjunction with the prior language requiring the Governor to publish a list of chemicals, "known to the state to cause cancer or reproductive toxicity."[30]

The Court then states that since chemicals may be included in IARC Group 2B based on less than sufficient evidence, they do not qualify for Proposition 65 listing on that basis.[31] "Although we concluded in Deukmejian that both human and animal carcinogens must be included on the Proposition 65 list, we caution that the standard remains known carcinogens."[32] The Court cites to the *Deukmejian* decision, saying:

> In Deukmejian, we observed: 'It is true that any substance within the scope of the federal [HCS]' (§ 6382, subd. (d)) includes chemicals other than known carcinogens. Section 25249.8, subdivision (a) and [Proposition 65] itself, however, are concerned only with those substances that authoritative bodies have concluded are known to cause cancer or reproductive toxicity. Thus, the initial list, and subsequent list published thereafter may not include all substances listed under HCS, but only those known carcinogens and reproductive toxicants listed there.[33]
>
> In Deukmejian, we repeatedly cautioned that the Governor's list and obligation under Proposition 65 is limited to substances which are known to cause cancer.[34]

The Court also looked to its decision in *Western Crop Protection Ass'n*. The issue there was whether OEHHA could list as reproductive toxicants chemicals on EPA's Toxics Release Inventory. The Court stated, "We thereafter concluded: 'OEHHA has the authority to examine the administrative record of the TRI procedure to determine if there is substantial evidence that the EPA has placed a chemical on the EPA list because it meets the state's criteria of causing . . .

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[30] *SIRC v. OEHHA* at 1087-1088.

[31] *Id.*

[32] *SIRC v. OEHHA* at 1094. (Italics in the original).

[33] *Id.* at 1098. (Citation omitted).

[34] *Id.* at 1100.

reproductive toxicity."[35] With respect to its decision in *Western Crop Protection Ass'n*, the *SIRC* Court said, "In other words, as long as there is sufficient evidence that the EPA placed a particular chemical on the TRI list based on criteria sufficient to satisfy Proposition 65's requirement that the chemical be known to cause reproductive toxicity, it does not matter that the federal standard may otherwise be broader and that other chemicals may have been placed on the TRI list based on a lesser showing."

When summarizing its holding in both *Deukmejian* and *Western Crop*, the Court said, "Our analysis in Western Crop, like that in Deukmejian, was based on a recognition that chemicals may be included on the Proposition 65 list only if there is a sufficient showing that they in fact cause cancer or reproductive toxicity. This interpretation is consistent with the legislative history underlying Proposition 65 and does not conflict with the minimum requirements language of section 25249.8, subdivision (a)." Hence, any listing under the Labor Code, regardless of the authoritative body list that OEHHA may use, requires that authoritative body to have based its listing decision on sufficient evidence demonstrating that the substance is known to cause cancer or reproductive toxicity.

V. Federal HCS Preempts the Proposed Rule

In adopting HCS 2012, OSHA explicitly acknowledged that:

> significant portions of the benefits of the rule . . . can only be achieved if the system used in the U.S. is consistently and uniformly applied throughout the nation and in conformance with the internationally harmonized system.[36]

As discussed elsewhere in these comments, it is possible that a chemical deemed a carcinogen by NTP or IARC will not be classified a carcinogen under the HCS based on a weight of evidence evaluation. A Proposition 65 listing stating otherwise, therefore, would be contrary to the classification developed under the federal HCS. Conflicting classifications would cause employees to receive conflicting messages about the chemical and would undermine the effectiveness and credibility of the hazard communication system.

A Proposition 65 listing presumably would require workplace training, signage and container labels communicating cancer warnings; yet the OSHA-required training, container label and SDSs for an interstate shipment would not. OSHA's concerns for these types of multiple schemes and inconsistent characterizations were expressed when the agency promulgated HCS 2012:

> The changes to the HCS will create a uniformity standard for the presentation of hazard information and, as such, will serve to improve the efficiency and effectiveness of the existing hazard communication system in the U.S., and to

[35] *Id.* at 1101.

[36] 77 Fed. Reg. at 17,575.

> reduce unnecessary barriers to trade. Hazard communication is currently addressed by many different international, national, and State authorities. . . . [T]hese existing requirements are not always consistent and often contain different definitions of hazards and varying provisions for what information is required on labels and safety data sheets. Complying with these different rules results in increased costs for employers with hazardous chemicals in their workplace and for chemical manufacturers, distributors, and transporters involved in international trade. In addition to these effects on businesses, the different existing requirements result in workplaces receiving chemicals with varying information, with potential adverse impacts on the safety and health of employees. The revisions to the OSHA HCS will standardize the hazard communication requirements for products used in U.S. workplaces, and thus provide employees with uniform and consistent hazard communication information. Secondarily, because these revisions will harmonize the U.S. system with international norms, they will facilitate international trade.[37]

OSHA works to eliminate conflicts between federal and state hazard communications standards consistent with Occupational Safety and Health Act (OSH Act) provisions designed to prevent those conflicts. To the extent it is applied to the workplace, a Proposition 65 listing would "stand as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," and make it "impossible" for a private party to comply with both state and Federal law.[38]

A preemption analysis begins with the Supremacy Clause of the U.S. Constitution, which declares that the "Constitution and the Laws of the United States . . . shall be the supreme Law of the Land."[39] As the U.S. Supreme Court has stated, "it has been settled that state law that conflicts with federal law is without effect."[40] The same holds true of state law that conflicts with federal regulation.[41] Courts look specifically to the intent expressed by Congress when adopting a statute as the "ultimate touchstone" of preemption analysis.[42] Such intent may be explicitly stated or implicitly contained in the statute's structure and purpose.[43]

While there are various types of preemption, at least one is relevant here – conflict preemption. Specifically, Federal law nullifies conflicting state law in at least two instances. The first type is where state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress" ("obstacle preemption").[44] The second type is where it is

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[37] *Id.* at 17,605.

[38] *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000) 166 F.3d 1236, affirmed.

[39] Article VI, Section 2, of the U.S. Constitution; *Cipollone v. Liggett Group, Inc.*, 112 S.Ct. 2608, 2617 (1992).

[40] *Id.*

[41] *Fidelity Fed. Sav. & Loan Ass'n v. De La Cuesta*, 458 U.S. 141, 153 (1982) ("Federal regulations have no less pre-emptive effect than federal statutes").

[42] *Cipollone v. Liggett Group, Inc*, at 2617.

[43] *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977).

[44] *Geier v. Am. Honda Motor Co., Inc.*, 529 U.S. 861, 873 (2000).

"impossible" for a private party to comply with both state and Federal law" ("impossibility preemption").[45]

Obstacle preemption would apply if OEHHA proceeds to finalize a listing. Under obstacle preemption, courts look specifically to the goals underlying a given regulatory scheme and ask whether the state law would frustrate the Federal agency's efforts to reach those goals. For example, the U.S. Supreme Court in *Geier* held that an injured motorist's design defect claim, which sought to hold a car manufacturer liable for failing to install a driver's side airbag, was preempted. The Court noted that Federal regulations at the time required manufacturers to install passive restraints in "some but not all" of their vehicles and provided a "range of choices among different passive restraint devices" to be "introduced gradually over time."[46] Citing to comments made by the Department of Transportation ("DoT") when issuing the regulation, the Court noted that its purpose was to "lower costs, overcome technical safety problems, encourage technological development, and win widespread consumer acceptance – all of which would promote [the regulation's] safety objectives."[47] In other words, DoT adopted a compromise between gradually forcing technological development and addressing immediate safety needs. The Court, not surprisingly, found that a state tort law which would require airbags in all vehicles "presented an obstacle to the variety and mix of devices that the federal regulation sought" and to the "gradual passive restraint phase-in that the federal regulation deliberately imposed."[48]

OSHA expressly sought in HCS 2012 to "create a uniformity standard for the presentation of hazard information." This uniformity will supplant "different existing requirements [that] result in workplaces receiving chemicals with varying information, with potential adverse impacts on the safety and health of employees," and "because these revisions will harmonize the U.S. system with international norms, they will facilitate international trade."[49]

All of this starts to unravel if California proceeds with the Labor Mechanism rule as proposed. Certain listings will undoubtedly create implied conflict preemption and the Proposition 65 requirements that would follow from a listing would frustrate the clear purpose of HCS 2012 to harmonize United States practices with the GHS.

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[45] *Cipollone v. Liggett Group, Inc*, at 2617.
[46] *Geier v. Am. Honda Motor Co., Inc.* at 874-75.
[47] *Id.* at 875.
[48] *Id.* at 881. *See also In re Bextra*, No. M: 05-1699 CRB, 2006 WL 2374742, at *9 (N.D. Cal. Aug. 16, 2006) (finding failure to warn tort claims involving an anti-inflammatory drug preempted under the Federal Food, Drug, and Cosmetic Act where class action plaintiffs argued for warnings that would have upset the policy choice made by the U.S. Food and Drug Administration to require the disclosure of known risks, but prohibit "defensive" labeling warning of unsubstantiated risks); *Blue Circle Cement, Inc. v. Bd. of Cnty. Comm'rs*, 917 F. Supp. 1514, 1519-20 (N.D. Okla. 1995) (holding local ordinance effectively prohibiting the burning of hazardous waste for energy was preempted by the Resource Conservation and Recovery Act's goal of "replac[ing] land disposal with advanced treatment, recycling, and incineration").
[49] 77 Fed. Reg. at 17,605.

VI. Conclusion

OEHHA is attempting to establish a Labor Code listing mechanism process that is outside the realm of what the California legislature contemplated or authorized when it enacted Labor Code section 6382(d). OEHHA also attempts to interpret the provisions of HCS 2012 in a manner that flies in the face of both the regulatory text and OSHA's intent in adopting HCS 2012. The text of the proposed regulation and the Initial Statement of Reasons issued by OEHHA to support the proposed rule reflect an inappropriate effort by the agency to rewrite both its statutory authority and the HCS 2012. As proposed, the Proposition 65 rule is inconsistent with the language, the intent and the underlying principles of the HCS 2012 and Labor Code section 6382(d).

In conclusion, the following points were not appropriately considered by OEHHA:

The Director's list is not a basis for listing a chemical under Proposition 65. Section 6382(d) added the reference to the federal HCS. The Director's list was established by section 6380. Hence, when section 6382(d) is read in context, the scope and relevance of section 6382(d) is limited to chemicals within the scope of the federal HCS.

As referenced by section A.6. of Appendix A of the HCS 2012, the only substances deemed to be carcinogens under HCS 2012 are the substances explicitly identified as carcinogens in OSHA's substance-specific standards found in 29 CFR part 1910, subpart Z (sections 1910.1001 to 1910. 1018, 1910.1020 to 1910.1029 , and 1910.1043 to 1910.1052). In contrast, section A.7. of Appendix A, when addressing the criteria for assessing reproductive toxicology, does not cross reference subpart Z. Accordingly, with the exception of the chemicals identified as carcinogens by OSHA under subpart Z, there is no referenced floor of chemicals within the scope of the HCS.

Chemicals do not fall within the scope of HCS 2012 merely because of an IARC Monograph or listing under the NTP RoC. The HCS 1994 reflected an outdated approach to hazard communication in providing that a chemical was to be considered a carcinogen for purposes of the HCS if found to be a carcinogen or potential carcinogen by IARC or if listed in the NTP ROC. Those provisions and that approach conflicted with the weight of evidence approach underlying the GHS and were eliminated from the HCS when HCS 2012 was adopted.

Appendix A of 29 C.F.R. section 1910.1200 provides specific, detailed criteria for each type of health hazard, which are to be applied by the manufacturer or employer in conducting the required self-classification of the chemical under a weight of evidence analysis. Appendix A does not require a manufacturer or importer to adopt the IARC or NTP findings. It merely permits a manufacturer or importer to rely on the NTP or IARC determination rather than conducting its own self-classification as to carcinogenicity.

Appendix D of 29 C.F.R. section 1910.1200 simply establishes a uniform format and content for SDSs. It requires the listing of IARC and NTP determinations as a piece of information, but it is not a classification determination. The criteria for determining whether a chemical is classified

as a health hazard are detailed in mandatory Appendix A to section 1910.1200. If the manufacturer or importer determined that a chemical classified as a carcinogen in an IARC monograph or listed in the NTP ROC did not pose any hazard covered by the HCS, it would not be a hazardous chemical, and no SDS would be required. Therefore, the IARC and NTP determinations would not be the factor that universally brought the chemical within the scope of HCS 2012, even if that phrase was erroneously misconstrued to apply where the substance was not deemed to be a carcinogen by the federal HCS.

Appendix F of 29 C.F.R. section 1910.1200 is a non-mandatory appendix that provides guidance on classification for carcinogenicity. While Appendix F refers to the cancer classification categories used by IARC and NTP, and the factors considered by IARC and NTP in making their determinations, it does not and cannot state that IARC and NTP findings are equivalent to the classification determination performed by those organizations. That is because NTP and IARC rely on strength of evidence rather than weight of evidence determinations.

In adopting HCS 2012, OSHA expressly sought to "create a uniformity standard for the presentation of hazard information" for the United States, harmonized with its global trading partners. OEHHA's proposed rule would conflict with and undermine the Federal objective by creating conflicting classifications, conflicting SDS, conflicting labels that would cause employees to receive conflicting training and communication about the hazards of the chemical and would undermine the effectiveness and credibility of the hazard communication system; thus federal preemption applies.

Finally, adoption of a rule providing that an individual self-classification determination by any importer or manufacturer -- regardless of evidence, qualifications or motive – would be binding on every employer in the State of California. It would represent a gross violation of due process, an improper delegation of government authority, and an arbitrary and capricious procedure that lacks any sound basis and an absurd approach open to the grossest forms of manipulation and abuse.

If OEHHA proceeds with a regulation to articulate the criteria it will follow in listing chemicals pursuant to the Labor Code references, it must do so consistently with the provisions of Proposition 65, the Labor Code, the federal HCS, and with the holdings of the courts *in AFL-CIO v. Deukmejian*, *Western Crop Protection Ass'n v. Davis*, and *SIRC v. OEHHA*. Accordingly, the references and chemicals that may be considered for listing are only as follows:

1. Substances listed as human or animal carcinogens by IARC as referenced in section 6382 (b)(1).
2. Chemicals for which OSHA has included cancer as a health hazard in 29 C.F.R. Part 1910, subpart Z.

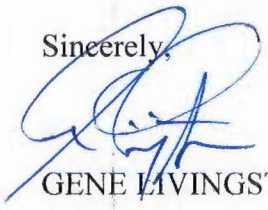
Stated in the affirmative, consistent with the 2012 changes to the OSHA HCS, the Labor Code listing mechanism referencing section 6382(d) continues to authorize OEHHA to list a substance as a carcinogen if the substance has been identified as a carcinogen in an OSHA substance-

specific standard. Listings based on IARC and NTP classifications, however, are no longer supported by reference to section 6382(d). The OSHA HCS has never served as a basis for listing substances based on reproductive toxicity. The 2012 amendments to OSHA HCS leave this unchanged.

Finally, to add a substance to the list of carcinogens under any of the listing mechanisms, the supporting toxicological evidence must be sufficient to demonstrate that the substance is a known carcinogen.[50]

The foregoing interpretation is consistent with the statutory language, existing case law, and the terms of the OSHA HCS. Any future proposal should be consistent with this statutory and regulatory framework.

Sincerely,



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[50] *See e.g., SIRC v. OEHHA*, Cal.App.3rd No. C0643d (2012); and *AFL-CIO v. Deukmejian*, 212 Cal.App.3d 425 (1989).

ATTACHMENT A

TO

COMMENTS

Attachment A

Excerpts from OSHA "Side-by-Side Comparison of OSHA's Existing Hazard Communication Standard vs. the Revised Hazard Communication Standard"

OSHA published a comparison of the old and revised provisions of the HCS, together with commentary, in a document titled "Side-by-Side Comparison of OSHA's Existing Hazard Communication Standard vs. the Revised Hazard Communication Standard" (Side-by-Side), U.S. Department of Labor, Occupational Safety & Health Administration, available at http://www.osha.gov/dsg/hazcom/side-by-side.html).

A review of changes to the language of the HCS makes it clear that HCS 2012 removed mandatory classification based on IARC or NTP classifications. Section 1910.1200(d) of the HCS governs hazard classification. As explained above, HCS 1994 section 1910.1200(d)(4) referenced the NTP Report on Carcinogens as part of the hazard determination process, but all the references to NTP have been deleted from section 1910.1200(d) of HCS 2012. Pertinent sections of the OSHA Side-by-Side comparison follow. **Old HCS or HCS 1994**	**Amended HCS or HCS 2012**
(d) *Hazard ~~determination.~~* ~~....~~ (d)(3) ~~The chemical manufacturer, importer or employer evaluating chemicals shall treat the following sources as establishing that the chemicals listed in them are hazardous:~~ ~~(d)(3)(i) 29 CFR part 1910, subpart Z, Toxic and Hazardous Substances, Occupational Safety and Health Administration (OSHA); or,~~ ~~(d)(3)(ii) "Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment," American Conference of Governmental Industrial Hygienists (ACGIH) (latest edition). The chemical manufacturer, importer, or employer is still~~	(d) *Hazard classification.* (d)(1) Chemical manufacturers and importers shall evaluate chemicals produced in their workplaces or imported by them to classify the chemicals in accordance with this section. For each chemical, the chemical manufacturer or importer shall determine the hazard classes, and where appropriate, the category of each class that apply to the chemical being classified. Employers are not required to classify chemicals unless they choose not to rely on the classification performed by the chemical manufacturer or importer for the chemical to satisfy this requirement.

~~responsible for evaluating the hazards associated with the chemicals in these source lists in accordance with the requirements of this standard.~~ ~~(d)(4) Chemical manufacturers, importers and employers evaluating chemicals shall treat the following sources as establishing that a chemical is a carcinogen or potential carcinogen for hazard communication purposes:~~ ~~(d)(4)(i) National Toxicology Program (NTP), "Annual Report on Carcinogens" (latest edition);~~ ~~(d)(4)(ii) International Agency for Research on Cancer (IARC) "Monographs" (latest editions); or~~ ~~(d)(4)(iii) 29 CFR part 1910, subpart Z, Toxic and Hazardous Substances, Occupational Safety and Health Administration.~~	(d)(2) Chemical manufacturers, importers or employers classifying chemicals shall identify and consider the full range of available scientific literature and other evidence concerning the potential hazards. There is no requirement to test the chemical to determine how to classify its hazards. Appendix A to §1910.1200 shall be consulted for classification of health hazards, and Appendix B to §1910.1200 shall be consulted for the classification of physical hazards.

The criteria for determining whether a chemical is classified as a health hazard are detailed in Appendix A to §1910.1200 -- Health Hazard Criteria.[51] The classification of carcinogens is addressed in Section A.6 of mandatory Appendix A to Section 1910.1200, *Health Hazard Criteria*. A review of the completely overhauled Appendix A demonstrates that the HCS now operates under a weight of evidence framework; NTP determinations are no longer treated as conclusive findings of carcinogenicity under the HCS.

Appendix A to Old HCS or HCS 1994	**Appendix A to Amended HCS or HCS 2012** [Figures, tables and footnotes omitted.]
For purposes of this section, any chemicals which meet any of the following definitions, as determined by the criteria set forth in Appendix B are health hazards. However, this is not intended to be an exclusive categorization scheme. If there are	A.6 CARCINOGENICITY A.6.1 Definitions Carcinogen means a substance or a mixture of

[51] *See*, page 9 of the attached Side-by-Side.

available scientific data that involve other animal species or test methods, they must also be evaluated to determine the applicability of the HCS. 1. "Carcinogen:" A chemical is considered to be a carcinogen if: (a) It has been evaluated by the International Agency for Research on Cancer (IARC), and found to be a carcinogen or potential carcinogen; or (b) It is listed as a carcinogen or potential carcinogen in the Annual Report on Carcinogens published by the National Toxicology Program (NTP) (latest edition); or, (c) It is regulated by OSHA as a carcinogen.	substances which induce cancer or increase its incidence. Substances and mixtures which have induced benign and malignant tumors in well-performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumor formation is not relevant for humans. Classification of a substance or mixture as posing a carcinogenic hazard is based on its inherent properties and does not provide information on the level of the human cancer risk which the use of the substance or mixture may represent. A.6.2 Classification Criteria for Substances A.6.2.1 For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional weight of evidence considerations. In certain instances, route-specific classification may be warranted. A.6.2.2 Classification as a carcinogen is made on the basis of evidence from reliable and acceptable methods, and is intended to be used for substances which have an intrinsic property to produce such toxic effects. The evaluations are to be based on all existing data, peer-reviewed published studies and additional data accepted by regulatory agencies. A.6.2.3 Carcinogen classification is a one-step, criterion-based process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories. A.6.2.4 Strength of evidence involves the enumeration of tumors in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between

	human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumors. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. (Guidance on consideration of important factors in the classification of carcinogenicity and a more detailed description of the terms ''limited'' and ''sufficient'' have been developed by the International Agency for Research on Cancer (IARC) and are provided in non-mandatory Appendix F). A.6.2.5 Weight of evidence: Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors should be considered that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans. The full list of factors that influence this determination is very lengthy, but some of the important ones are considered here. A.6.2.5.1 These factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumor findings and the other factors in a case-by-case manner. A.6.2.5.2 Some important factors which may be taken into consideration, when assessing the overall level of concern are:

	(a) Tumor type and background incidence; (b) Multisite responses; (c) Progression of lesions to malignancy; (d) Reduced tumor latency; Additional factors which may increase or decrease the level of concern include: (e) Whether responses are in single or both sexes; (f) Whether responses are in a single species or several species; (g) Structural similarity or not to a substance(s) for which there is good evidence of carcinogenicity; (h) Routes of exposure; (i) Comparison of absorption, distribution, metabolism and excretion between test animals and humans; (j) The possibility of a confounding effect of excessive toxicity at test doses; and, (k) Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression. Mutagenicity: It is recognized that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity in vivo may indicate that a substance has a potential for carcinogenic effects. A.6.2.5.3 A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B, or Category 2 based on tumor data from a structural analogue together with substantial support from consideration of other important

	factors such as formation of common significant metabolites, e.g., for benzidine congener dyes. A.6.2.5.4 The classification should also take into consideration whether or not the substance is absorbed by a given route(s); or whether there are only local tumors at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity. A.6.2.5.5 It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e., structure activity relationship, is taken into consideration when undertaking classification. A.6.3 Classification Criteria for Mixtures A.6.3.1 The mixture shall be classified as a carcinogen when at least one ingredient has been classified as a Category 1 or Category 2 carcinogen and is present at or above the appropriate cut-off value/concentration limit as shown in Table A.6.1. A.6.3.2 Classification of Mixtures When Data Are Available for the Complete Mixture A mixture may be classified based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g., statistical analysis, test sensitivity) of carcinogenicity test systems. A.6.3.3 Classification of Mixtures When Data Are Not Available for the Complete Mixture: Bridging Principles Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient

	data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution; Batching; and Substantially similar mixtures. A.6.4 Classification of Carcinogenicity A.6.4.1 Chemical manufacturers, importers and employers evaluating chemicals may treat the following sources as establishing that a substance is a carcinogen or potential carcinogen for hazard communication purposes in lieu of applying the criteria described herein: A.6.4.1.1 National Toxicology Program (NTP), ''Report on Carcinogens'' (latest edition); A.6.4.1.2 International Agency for Research on Cancer (IARC) ''Monographs on the Evaluation of Carcinogenic Risks to Humans'' (latest editions) A.6.4.2 Where OSHA has included cancer as a health hazard to be considered by classifiers for a chemical covered by 29 CFR part 1910, Subpart Z, Toxic and Hazardous Substances, chemical manufacturers, importers, and employers shall classify the chemical as a carcinogen. 8. *See Non-mandatory Appendix F for further guidance regarding hazard classification for carcinogenicity and how to relate carcinogenicity classification information from IARC and NTP to GHS.*

ATTACHMENT B

TO

COMMENTS

UNITED STATES DEPARTMENT OF LABOR

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Regulations (Standards - 29 CFR) - Table of Contents

• **Part Number:**	1910
• **Part Title:**	Occupational Safety and Health Standards
• **Subpart:**	Z
• **Subpart Title:**	Toxic and Hazardous Substances
• **Standard Number:**	1910.1200 App A
• **Title:**	Health Hazard Criteria (Mandatory)

Appendix A TO §1910.1200—Health Hazard Criteria (Mandatory)

A.0 GENERAL CLASSIFICATION CONSIDERATIONS

A.0.1 Classification

A.0.1.1 The term "hazard classification" is used to indicate that only the intrinsic hazardous properties of chemicals are considered. Hazard classification incorporates three steps:

(a) identification of relevant data regarding the hazards of a chemical;

(b) subsequent review of those data to ascertain the hazards associated with the chemical;

(c) determination of whether the chemical will be classified as hazardous and the degree of hazard.

A.0.1.2 For many hazard classes, the criteria are semi quantitative or qualitative and expert judgment is required to interpret the data for classification purposes.

A.0.2 Available data, test methods and test data quality

A.0.2.1 There is no requirement for testing chemicals.

A.0.2.2 The criteria for determining health hazards are test method neutral, i.e., they do not specify particular test methods, as long as the methods are scientifically validated.

A.0.2.3 The term "scientifically validated" refers to the process by which the reliability and the relevance of a procedure are established for a particular purpose. Any test that determines hazardous properties, which is conducted according to recognized scientific principles, can be used for purposes of a hazard determination for health hazards. Test conditions need to be standardized so that the results are reproducible with a given substance, and the standardized test yields "valid" data for defining the hazard class of concern.

A.0.2.4 Existing test data are acceptable for classifying chemicals, although expert judgment also may be needed for classification purposes.

A.0.2.5 The effect of a chemical on biological systems is influenced, by the physico-chemical properties of the substance and/or ingredients of the mixture and the way in which ingredient substances are biologically available. A chemical need not be classified when it can be shown by conclusive experimental data from scientifically validated test methods that the chemical is not biologically available.

A.0.2.6 For classification purposes, epidemiological data and experience on the effects of chemicals on humans (e.g., occupational data, data from accident databases) shall be taken into account in the evaluation of human health hazards of a chemical.

A.0.3 Classification based on weight of evidence

A.0.3.1 For some hazard classes, classification results directly when the data satisfy the criteria. For others, classification of a chemical shall be determined on the basis of the total weight of evidence using expert judgment. This means that all available information bearing on the classification of hazard shall be considered together, including the results of valid in vitro tests, relevant animal data, and human experience such as epidemiological and clinical studies and well-documented case reports and observations.

A.0.3.2 The quality and consistency of the data shall be considered. Information on chemicals related to the material being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. Both positive and negative results shall be considered together in a single weight-of-evidence determination.

A.0.3.3 Positive effects which are consistent with the criteria for classification, whether seen in humans or animals, shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Reliable, good quality human data shall generally have precedence over other data. However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, or to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data.

A.0.3.4 Route of exposure, mechanistic information, and metabolism studies are pertinent to determining the relevance of an effect in humans. When such information raises doubt about relevance in humans, a lower classification may be warranted. When there is scientific evidence demonstrating that the mechanism or mode of action is not relevant to humans, the chemical should not be classified.

A.0.3.5 Both positive and negative results are considered together in the weight of evidence determination. However, a single positive study performed according to good

scientific principles and with statistically and biologically significant positive results may justify classification.

A.0.4 Considerations for the classification of mixtures

A.0.4.1 For most hazard classes, the recommended process of classification of mixtures is based on the following sequence:

(a) Where test data are available for the complete mixture, the classification of the mixture will always be based on those data;

(b) Where test data are not available for the mixture itself, the bridging principles designated in each health hazard chapter of this appendix shall be considered for classification of the mixture;

(c) If test data are not available for the mixture itself, and the available information is not sufficient to allow application of the above-mentioned bridging principles, then the method(s) described in each chapter for estimating the hazards based on the information known will be applied to classify the mixture (e.g., application of cut-off values/concentration limits).

A.0.4.2 An exception to the above order or precedence is made for Carcinogenicity, Germ Cell Mutagenicity, and Reproductive Toxicity. For these three hazard classes, mixtures shall be classified based upon information on the ingredient substances, unless on a case-by-case basis, justification can be provided for classifying based upon the mixture as a whole. See chapters A.5, A.6, and A.7 for further information on case-by-case bases.

A.0.4.3 Use of cut-off values/concentration limits

A.0.4.3.1 When classifying an untested mixture based on the hazards of its ingredients, cut-off values/concentration limits for the classified ingredients of the mixture are used for several hazard classes. While the adopted cut-off values/concentration limits adequately identify the hazard for most mixtures, there may be some that contain hazardous ingredients at lower concentrations than the specified cut-off values/concentration limits that still pose an identifiable hazard. There may also be cases where the cut-off value/concentration limit is considerably lower than the established non-hazardous level for an ingredient.

A.0.4.3.2 If the classifier has information that the hazard of an ingredient will be evident (i.e., it presents a health risk) below the specified cut-off value/concentration limit, the mixture containing that ingredient shall be classified accordingly.

A.0.4.3.3 In exceptional cases, conclusive data may demonstrate that the hazard of an ingredient will not be evident (i.e., it does not present a health risk) when present at a level above the specified cut-off value/concentration limit(s). In these cases the mixture may be classified according to those data. The data must exclude the possibility that the ingredient will behave in the mixture in a manner that would increase the hazard over that of the pure substance. Furthermore, the mixture must not contain ingredients that would affect that determination.

A.0.4.4 Synergistic or antagonistic effects

When performing an assessment in accordance with these requirements, the evaluator must take into account all available information about the potential occurrence of synergistic effects among the ingredients of the mixture. Lowering classification of a mixture to a less hazardous category on the basis of antagonistic effects may be done only if the determination is supported by sufficient data.

A.0.5 Bridging principles for the classification of mixtures where test data are not available for the complete mixture

A.0.5.1 Where the mixture itself has not been tested to determine its toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data shall be used in accordance with the following bridging principles, subject to any specific provisions for mixtures for each hazard class. These principles ensure that the classification process uses the available data to the greatest extent possible in characterizing the hazards of the mixture.

A.0.5.1.1 Dilution

For mixtures classified in accordance with A.1 through A.10 of this Appendix, if a tested mixture is diluted with a diluent that has an equivalent or lower toxicity classification than the least toxic original ingredient, and which is not expected to affect the toxicity of other ingredients, then:

(a) the new diluted mixture shall be classified as equivalent to the original tested mixture; or

(b) for classification of acute toxicity in accordance with A.1 of this Appendix, paragraph A.1.3.6 (the additivity formula) shall be applied.

A.0.5.1.2 Batching

For mixtures classified in accordance with A.1 through A.10 of this Appendix, the toxicity of a tested production batch of a mixture can be assumed to be substantially equivalent to that of another untested production batch of the same mixture, when produced by or under the control of the same *chemical manufacturer*, unless there is reason to believe there is significant variation such that the toxicity of the untested batch has changed. If the latter occurs, a new classification is necessary.

A.0.5.1.3 Concentration of mixtures

For mixtures classified in accordance with A.1, A.2, A.3, A.8, A.9, or A.10 of this Appendix, if a tested mixture is classified in Category 1, and the concentration of the ingredients of the tested mixture that are in Category 1 is increased, the resulting untested mixture shall be classified in Category 1.

A.0.5.1.4 Interpolation within one toxicity category

For mixtures classified in accordance with A.1, A.2, A.3, A.8, A.9, or A.10 of this Appendix, for three mixtures (A, B and C) with identical ingredients, where mixtures A and B have been tested and are in the same toxicity category, and where untested mixture C has the same toxicologically active ingredients as mixtures A and B but has concentrations of toxicologically active ingredients intermediate to the concentrations in mixtures A and B, then mixture C is assumed to be in the same toxicity category as A and B.

A.0.5.1.5 Substantially similar mixtures

For mixtures classified in accordance with A.1 through A.10 of this Appendix, given the following set of conditions:

(a) Where there are two mixtures: (i) A + B;
(ii) C + B;

(b) the concentration of ingredient B is essentially the same in both mixtures;

(c) the concentration of ingredient A in mixture (i) equals that of ingredient C in mixture (ii);

(d) and data on toxicity for A and C are available and substantially equivalent; i.e., they are in the same hazard category and are not expected to affect the toxicity of B; then

If mixture (i) or (ii) is already classified based on test data, the other mixture can be assigned the same hazard category.

A.0.5.1.6 Aerosols

For mixtures classified in accordance with A.1, A.2, A.3, A.4, A.8, or A.9 of this Appendix, an aerosol form of a mixture shall be classified in the same hazard category as the tested, non-aerosolized form of the mixture, provided the added propellant does not affect the toxicity of the mixture when spraying.

A.1 ACUTE TOXICITY

A.1.1 Definition

Acute toxicity refers to those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.

A.1.2 Classification criteria for substances

A.1.2.1 Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric cut-off criteria as shown in Table A.1.1. Acute toxicity values are expressed as (approximate) LD50 (oral, dermal) or LC50 (inhalation) values or as acute toxicity estimates (ATE). See the footnotes following Table A.1.1 for further explanation on the application of these values.

Table A.1.1: Acute toxicity hazard categories and acute toxicity estimate (ATE) values defining the respective categories

Exposure route	Category 1	Category 2	Category 3	Category 4
Oral (mg/kg bodyweight) *see: Note (a)* *Note (b)*	≤ 5	>5 and ≤ 50	>50 and ≤ 300	>300 and ≤ 2000
Dermal (mg/kg bodyweight) *see: Note (a)* *Note (b)*	≤ 50	>50 and ≤ 200	>200 and ≤ 1000	>1000 and ≤ 2000
Inhalation - Gases (ppmV) *see: Note (a)* *Note (b)* *Note (c)*	≤ 100	>100 and ≤ 500	>500 and ≤ 2500	>2500 and ≤ 20000
Inhalation - Vapors (mg/l) *see: Note (a)* *Note (b)* *Note (c)* *Note (d)*	≤ 0.5	>0.5 and ≤ 2.0	>2.0 and ≤ 10.0	>10.0 and ≤ 20.0
Inhalation – Dusts and Mists (mg/l) *see: Note (a)* *Note (b)* *Note (c)*	≤ 0.05	>0.05 and ≤ 0.5	>0.5 and ≤ 1.0	>1.0 and ≤ 5.0

Note: Gas concentrations are expressed in parts per million per volume (ppmV).

Notes to Table A.1.1:

(a) The acute toxicity estimate (ATE) for the classification of a substance is derived using the LD_{50}/LC_{50} where available;

(b) The acute toxicity estimate (ATE) for the classification of a substance or ingredient in a mixture is derived using:

(i) the LD_{50}/LC_{50} where available. Otherwise,

(ii) the appropriate conversion value from Table 1.2 that relates to the results of a range test, or

(iii) the appropriate conversion value from Table 1.2 that relates to a classification category;

(c) Inhalation cut-off values in the table are based on 4 hour testing exposures. Conversion of existing inhalation toxicity data which has been generated according to 1 hour exposure is achieved by dividing by a factor of 2 for gases and vapors and 4 for dusts and mists;

(d) For some substances the test atmosphere will be a vapor which consists of a combination of liquid and gaseous phases. For other substances the test atmosphere may consist of a vapor which is nearly all the gaseous phase. In these latter cases, classification is based on ppmV as follows: Category 1 (100 ppmV), Category 2 (500 ppmV), Category 3 (2500 ppmV), Category 4 (20000 ppmV).

The terms "dust", "mist" and "vapor" are defined as follows:

(i) Dust: solid particles of a substance or mixture suspended in a gas (usually air);

(ii) Mist: liquid droplets of a substance or mixture suspended in a gas (usually air);

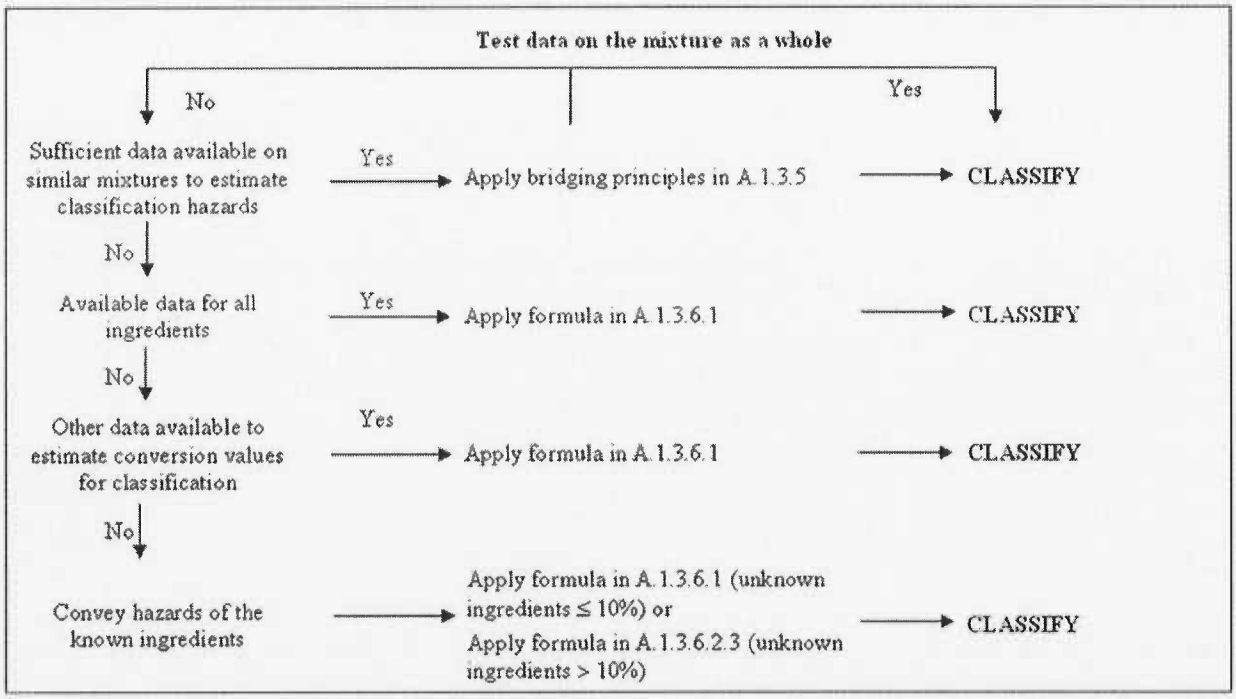
(iii) Vapor: the gaseous form of a substance or mixture released from its liquid or solid state.

A.1.2.3 The preferred test species for evaluation of acute toxicity by the oral and inhalation routes is the rat, while the rat or rabbit are preferred for evaluation of acute dermal toxicity. Test data already generated for the classification of chemicals under existing systems should be accepted when reclassifying these chemicals under the harmonized system. When experimental data for acute toxicity are available in several animal species, scientific judgment should be used in selecting the most appropriate LD50 value from among scientifically validated tests.

A.1.3 Classification criteria for mixtures

A.1.3.1 The approach to classification of mixtures for acute toxicity is tiered, and is dependent upon the amount of information available for the mixture itself and for its ingredients. The flow chart of Figure A.1.1 indicates the process that must be followed:

Figure A.1.1: Tiered approach to classification of mixtures for acute toxicity



A.1.3.2 Classification of mixtures for acute toxicity may be carried out for each route of exposure, but is only required for one route of exposure as long as this route is followed (estimated or tested) for all ingredients and there is no relevant evidence to suggest acute toxicity by multiple routes. When there is relevant evidence of acute toxicity by multiple routes of exposure, classification is to be conducted for all appropriate routes of exposure. All available information shall be considered. The pictogram and signal word used shall reflect the most severe hazard category; and all relevant hazard statements shall be used.

A.1.3.3 For purposes of classifying the hazards of mixtures in the tiered approach:

(a) The "relevant ingredients" of a mixture are those which are present in concentrations ≥ 1% (weight/weight for solids, liquids, dusts, mists and vapors and volume/volume for gases). If there is reason to suspect that an ingredient present at a concentration < 1% will affect classification of the mixture for acute toxicity, that ingredient shall also be considered relevant. Consideration of ingredients present at a concentration < 1% is particularly important when classifying untested mixtures which contain ingredients that are classified in Category 1 and Category 2;

(b) Where a classified mixture is used as an ingredient of another mixture, the actual or derived acute toxicity estimate (ATE) for that mixture is used when calculating the classification of the new mixture using the formulas in A.1.3.6.1 and A.1.3.6.2.4.

(c) If the converted acute toxicity point estimates for all ingredients of a mixture are within the same category, then the mixture should be classified in that category.

(d) When only range data (or acute toxicity hazard category information) are available for ingredients in a mixture, they may be converted to point estimates in accordance with Table A.1.2 when calculating the classification of the new mixture using the formulas in A.1.3.6.1 and A.1.3.6.2.4.

A.1.3.4 Classification of mixtures where acute toxicity test data are available for the complete mixture

Where the mixture itself has been tested to determine its acute toxicity, it is classified according to the same criteria as those used for substances, presented in Table A.1.1. If test data for the mixture are not available, the procedures presented below must be followed.

A.1.3.5 Classification of mixtures where acute toxicity test data are not available for the complete mixture: bridging principles

A.1.3.5.1 Where the mixture itself has not been tested to determine its acute toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of

this Appendix: Dilution, Batching, Concentration of mixtures, Interpolation within one toxicity category, Substantially similar mixtures, and Aerosols.

A.1.3.6 Classification of mixtures based on ingredients of the mixture (additivity formula)

A.1.3.6.1 Data available for all ingredients

The acute toxicity estimate (ATE) of ingredients is considered as follows:

(a) Include ingredients with a known acute toxicity, which fall into any of the acute toxicity categories, or have an oral or dermal LD50 greater than 2000 but less than or equal to 5000 mg/kg body weight (or the equivalent dose for inhalation);

(b) Ignore ingredients that are presumed not acutely toxic (e.g., water, sugar);

(c) Ignore ingredients if the data available are from a limit dose test (at the upper threshold for Category 4 for the appropriate route of exposure as provided in Table A.1.1) and do not show acute toxicity.

Ingredients that fall within the scope of this paragraph are considered to be ingredients with a known acute toxicity estimate (ATE). See note (b) to Table A.1.1 and paragraph A.1.3.3 for appropriate application of available data to the equation below, and paragraph A.1.3.6.2.4.

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below for oral, dermal or inhalation toxicity:

$$\frac{100}{ATEmix} = \sum_{n} \frac{Ci}{ATE_{i}}$$

where:
Ci = concentration of ingredient i
n ingredients and i is running from 1 to n
ATEi = acute toxicity estimate of ingredient i.

A.1.3.6.2 Data are not available for one or more ingredients of the mixture

A.1.3.6.2.1 Where an ATE is not available for an individual ingredient of the mixture, but available information provides a derived conversion value, the formula in A.1.3.6.1 may be applied. This information may include evaluation of:

(a) Extrapolation between oral, dermal and inhalation acute toxicity estimates. Such an evaluation requires appropriate pharmacodynamic and pharmacokinetic data;

(b) Evidence from human exposure that indicates toxic effects but does not provide lethal dose data;

(c) Evidence from any other toxicity tests/assays available on the substance that indicates toxic acute effects but does not necessarily provide lethal dose data; or

(d) Data from closely analogous substances using structure/activity relationships.

A.1.3.6.2.2 This approach requires substantial supplemental technical information, and a highly trained and experienced expert, to reliably estimate acute toxicity. If sufficient information is not available to reliably estimate acute toxicity, proceed to the provisions of A.1.3.6.2.3.

A.1.3.6.2.3 In the event that an ingredient with unknown acute toxicity is used in a mixture at a concentration ≥ 1%, and the mixture has not been classified based on testing of the mixture as a whole, the mixture cannot be attributed a definitive acute toxicity estimate. In this situation the mixture is classified based on the known ingredients only. (Note: A statement that x percent of the mixture consists of ingredient(s) of unknown toxicity is required on the label and safety data sheet in such cases; see Appendix C, Allocation of Label Elements and Appendix D, Safety Data Sheets.)

Where an ingredient with unknown acute toxicity is used in a mixture at a concentration ≥ 1%, and the mixture is not classified based on testing of the mixture as a whole, a statement that X% of the mixture consists of ingredient(s) of unknown acute toxicity is required on the label and safety data sheet in such cases; see Appendix C, Allocation of Label Elements and Appendix D, Safety Data Sheets.)

A.1.3.6.2.4 If the total concentration of the relevant ingredient(s) with unknown acute toxicity is ≤ 10% then the formula presented in A.1.3.6.1 must be used. If the total concentration of the relevant ingredient(s) with unknown acute toxicity is < 10%, the formula presented in A.1.3.6.1 is corrected to adjust for the percentage of the unknown ingredient(s) as follows:

$$\frac{100-(\sum C_{unknown} \text{ if } >10\%)}{ATE_{mix}} = \sum_{n} \frac{Ci}{ATE_{i}}$$

Table A.1.2: Conversion from experimentally obtained acute toxicity range values (or acute toxicity hazard categories) to acute toxicity point estimates for use in the formulas for the classification of mixtures

Exposure routes	Classification category or experimentally obtained acute toxicity range estimate			Converted Acute Toxicity point estimate
Oral (mg/kg bodyweight)	0	< Category 1 ≤	5	0.5
	5	< Category 2 ≤	50	5
	50	< Category 3 ≤	300	100
	300	< Category 4 ≤	2000	500
Dermal (mg/kg bodyweight)				5
	0	< Category 1 ≤	50	50
	50	< Category 2 ≤	200	300

	200 1000	< Category 3 ≤ < Category 4 ≤	1000 2000	1100
Gases (ppmV)	0 100 500 2500	< Category 1 ≤ < Category 2 ≤ < Category 3 ≤ < Category 4 ≤	100 500 2500 20000	10 100 700 4500
Vapors (mg/l)	0 0.5 2.0 10.0	< Category 1 ≤ < Category 2 ≤ < Category 3 ≤ < Category 4 ≤	0.5 2.0 10.0 20.0	0.05 0.5 3 11
Dust/mist (mg/l)	0 0.05 0.5 1.0	< Category 1 ≤ < Category 2 ≤ < Category 3 ≤ < Category 4 ≤	0.05 0.5 1.0 5.0	0.005 0.05 0.5 1.5

Note: Gas concentrations are expressed in parts per million per volume (ppmV).

A.2 SKIN CORROSION/IRRITATION

A.2.1 Definitions and general considerations

A.2.1.1 *Skin corrosion* is the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours. Corrosive reactions are typified by ulcers, bleeding, bloody scabs, and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia, and scars. Histopathology should be considered to evaluate questionable lesions.

Skin irritation is the production of reversible damage to the skin following the application of a test substance for up to 4 hours.

A.2.1.2 Skin corrosion/irritation shall be classified using a tiered approach as detailed in figure A.2.1. Emphasis shall be placed upon existing human data (See A.0.2.6), followed by other sources of information. Classification results directly when the data satisfy the criteria in this section. In case the criteria cannot be directly applied, classification of a substance or a mixture is made on the basis of the total weight of evidence (See A.0.3.1). This means that all available information bearing on the determination of skin corrosion/irritation is considered together, including the results of appropriate scientifically validated in-vitro tests, relevant animal data, and human data such as epidemiological and clinical studies and well-documented case reports and observations.

A.2.2 Classification criteria for substances using animal test data

A.2.2.1 Corrosion

A.2.2.1.1 A corrosive substance is a chemical that produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis, in at least 1 of 3 tested animals after exposure up to a 4-hour duration. Corrosive reactions are typified by ulcers, bleeding, bloody scabs and, by the end of observation at 14 days, by discoloration due to blanching of the skin, complete areas of alopecia and scars. Histopathology should be considered to discern questionable lesions.

A.2.2.1.2 Three sub-categories of Category 1 are provided in Table A.2.1, all of which shall be regulated as Category 1.

Table A.2.1: Skin corrosion category and sub-categories

Category 1: Corrosive	Corrosive sub-categories	Corrosive in ≥ 1 of 3 animals	
		Exposure	Observation
	1A	≤ 3 min	≤ 1 h
	1B	> 3 min ≤ 1 h	≤ 14 days
	1C	> 1 h ≤ 4 h	≤ 14 days

A.2.2.2 Irritation

A.2.2.2.1 A single irritant category (Category 2) is presented in the Table A.2.2. The major criterion for the irritant category is that at least 2 tested animals have a mean score of ≥ 2.3 ≥ 4.0.

Table A.2.2 Skin irritation category

	Criteria
Irritant (Category 2)	(1) Mean value of ≥ 2.3 ≥ 4.0 for erythema/eschar or for edema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or (2) Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or (3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.

A.2.2.2.2 Animal irritant responses within a test can be quite variable, as they are with corrosion. A separate irritant criterion accommodates cases when there is a significant irritant response but less than the mean score criterion for a positive test. For example, a substance might be designated as an irritant if at least 1 of 3 tested animals shows a very elevated mean score throughout the study, including lesions persisting at the end of an observation period of normally 14 days. Other responses could also fulfil this criterion. However, it should be ascertained that the responses are the result of chemical exposure. Addition of this criterion increases the sensitivity of the classification system.

A.2.2.2.3. Reversibility of skin lesions is another consideration in evaluating irritant responses. When inflammation persists to the end of the observation period in 2 or more test animals, taking into consideration alopecia (limited area), hyperkeratosis, hyperplasia and scaling, then a chemical should be considered to be an irritant.

A.2.3 Classification Criteria for Substances Using Other Data Elements

A.2.3.1 Existing human and animal data including information from single or repeated exposure should be the first line of analysis, as they give information directly relevant to effects on the skin. If a substance is highly toxic by the dermal route, a skin corrosion/irritation study may not be practicable since the amount of test substance to be applied would considerably exceed the toxic dose and, consequently, would result in the death of the animals. When observations are made of skin corrosion/irritation in acute toxicity studies and are observed up through the limit dose, these data may be used for classification provided that the dilutions used and species tested are equivalent. *In vitro* alternatives that have been scientifically validated shall be used to make classification decisions. Solid substances (powders) may become corrosive or irritant when moistened or in contact with moist skin or mucous membranes. Likewise, pH extremes like ≤ 2 and ≥ 11.5 may indicate skin effects, especially when associated with significant buffering capacity. Generally, such substances are expected to produce significant effects on the skin. In the absence of any other information, a substance is considered corrosive (Skin Category 1) if it has a pH ≤ 2 or a pH ≥ 11.5. However, if consideration of alkali/acid reserve suggests the substance or mixture may not be corrosive despite the low or high pH value, then further evaluation may be necessary. In some cases enough information may be available from structurally related compounds to make classification decisions.

A.2.3.2 A *tiered approach* to the evaluation of initial information shall be used (Figure A.2.1) recognizing that all elements may not be relevant in certain cases.

A.2.3.3 The tiered approach explains how to organize information on a substance and to make a weight-of-evidence decision about hazard assessment and hazard classification.

A.2.3.4 All the above information that is available on a substance shall be evaluated. Although information might be gained from the evaluation of single parameters within a tier, there is merit in considering the totality of existing information and making an overall weight of evidence determination. This is especially true when there is information available on some but not all parameters. Emphasis shall be placed upon existing human experience and data, followed by animal experience and testing data, followed by other sources of information, but case-by-case determinations are necessary.

Figure A.2.1: Tiered evaluation of skin corrosion and irritation potential

Step	Parameter	Finding	Conclusion
1a	Existing human or animal data[1]	Skin corrosive	Category 1[2]
	↓ Not corrosive or no data		
1b	Existing human or animal data[1]	Skin irritant	Category 2[2]
	↓ Not an irritant or no data		
1c	Existing human or animal data[1]	Not a skin corrosive or skin irritant	Not classified
	↓ No/Insufficient data		
2:	Other, existing skin data in animals[3]	Skin corrosive Skin irritant	Category 1[2] Category 2[2]
	↓ No/Insufficient data		
3:	Existing skin corrosive *ex vivo / in vitro* data[4]	Positive: Skin corrosive	Category 1[2]
	↓ Not corrosive or no data		
	Existing skin irritation *ex vivo / in vitro* data[4]	Positive: Skin irritant Negative: Not a skin irritant[5]	Category 2[2] Not classified
	↓ No/Insufficient data		
4:	pH-Based assessment (with consideration of buffering capacity of the chemical, or no buffering capacity data)[5]	pH ≤ 2 or ≥ 11.5	Category 1[2]
	↓ Not a pH extreme, No pH data or extreme pH with low/no buffering capacity		
5:	Validated Structure/Activity Relationship (SAR) models	Skin corrosive Skin irritant	Category 1[2] Category 2[2]
	↓ No/Insufficient data		
6:	Consideration of the total Weight of Evidence[6]	Skin corrosive Skin irritant	Category 1[2] Category 2[2]
	↓ No concern based on consideration of the sum of available data		
7:	Not Classified		Not classified

Notes to Figure A.2.1:

1. *Evidence of existing human or animal data may be derived from single or repeated exposure(s) in occupational, consumer, transportation, or emergency response scenarios; from ethically-conducted human clinical studies; or from purposely-generated data from animal studies conducted according to scientifically validated test methods (at present, there is no internationally accepted test method for human skin irritation testing).*

2. *Classify in the appropriate harmonized category, as shown in Tables A.2.1 and A.2.2.*

3. *Pre-existing animal data (e.g. from an acute dermal toxicity test or a sensitisation test) should be carefully reviewed to determine if sufficient skin corrosion/irritation evidence is available through other, similar information. For example, classification/categorization may be done on the basis of whether a chemical has or has not produced any skin irritation in an acute dermal toxicity test in animals at the limit dose, or produces very toxic effects in an acute dermal toxicity test in animals. In the latter case, the chemical would be classified as being very hazardous by the dermal route for acute toxicity, and it would be moot whether the chemical is also irritating or corrosive on the skin. It should be kept in mind in evaluating acute dermal toxicity information that the reporting of dermal lesions may be incomplete, testing and observations may be made on a species other than the rabbit, and species may differ in sensitivity in their responses.*

4. *Evidence from studies using scientifically validated protocols with isolated human/animal tissues or other, non-tissue-based, though scientifically validated, protocols should be assessed. Examples of scientifically validated test methods for skin corrosion include OECD TG 430 (Transcutaneous Electrical Resistance Test (TER)), 431 (Human Skin Model Test), and 435 (Membrane Barrier Test Method). OECD TG 439 (Reconstructed Human Epidermis Test Method) is a scientifically validated in vitro*

test method for skin irritation.

5. *Measurement of pH alone may be adequate, but assessment of acid or alkali reserve (buffering capacity) would be preferable. Presently, there is no scientifically validated and internationally accepted method for assessing this parameter.*

6. *All information that is available on a chemical should be considered and an overall determination made on the total weight of evidence. This is especially true when there is conflict in information available on some parameters. Professional judgment should be exercised in making such a determination.*

A.2.4 Classification criteria for mixtures

A.2.4.1 Classification of mixtures when data are available for the complete mixture

A.2.4.1.1 The mixture shall be classified using the criteria for substances (See A.2.3).

A.2.4.2 Classification of mixtures when data are not available for the complete mixture: bridging principles

A.2.4.2.1 Where the mixture itself has not been tested to determine its skin corrosion/irritation, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles, as found in paragraph A.0.5 of this Appendix: Dilution, Batching, Concentration of mixtures, Interpolation within one toxicity category, Substantially similar mixtures, and Aerosols.

A.2.4.3 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A.2.4.3.1 For purposes of classifying the skin corrosion/irritation hazards of mixtures in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥1% (weight/weight for solids, liquids, dusts, mists and vapors and volume/volume for gases.) If the classifier has reason to suspect that an ingredient present at a concentration <1% will affect classification of the mixture for skin corrosion/irritation, that ingredient shall also be considered relevant.

A.2.4.3.2 In general, the approach to classification of mixtures as irritant or corrosive to skin when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant ingredient contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive ingredients when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as corrosive or irritant when the sum of the concentrations of such ingredients exceeds a cut-off value/concentration limit.

A.2.4.3.3 Table A.2.3 below provides the cut-off value/concentration limits to be used to determine if the mixture is considered to be an irritant or a corrosive to the skin.

A.2.4.3.4 Particular care shall be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in A.2.4.3.1 and A.2.4.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases the pH should be used as classification criteria since pH will be a better indicator of corrosion than the concentration limits of Table A.2.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach shown in Table A.2.3, due to chemical characteristics that make this approach unworkable, should be classified as Skin Category 1 if it contains ≥ 1% of a corrosive ingredient and as Skin Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table A.2.3 does not apply is summarized in Table A.2.4 below.

A.2.4.3.5 On occasion, reliable data may show that the skin corrosion/irritation of an ingredient will not be evident when present at a level above the generic concentration cut-off values mentioned in Tables A.2.3 and A.2.4. In these cases the mixture could be classified according to those data (See *Use of cut-off values/concentration limits*, paragraph A.0.4.3 of this Appendix).

A.2.4.3.6 If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture shall be classified accordingly (See *Use of cut-off values /concentration limits*, paragraph A.0.4.3 of this Appendix).

Table A.2.3: Concentration of ingredients of a mixture classified as skin Category 1 or 2 that would trigger classification of the mixture as hazardous to skin (Category 1 or 2)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Skin corrosive	Skin irritant
	Category 1	Category 2
Skin Category 1	≥ 5%	≥ 1% but < 5%
Skin Category 2		≥ 10%
(10 x Skin Category 1) + Skin Category 2		≥ 10%

Table A.2.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to skin

Ingredient:	Concentration:	Mixture classified as: Skin
Acid with pH ≤ 2	≥ 1%	Category 1
Base with pH ≥ 11.5	≥ 1%	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

A.3 SERIOUS EYE DAMAGE /EYE IRRITATION

A.3.1 Definitions and general considerations

A.3.1.1 *Serious eye damage* is the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application.

Eye irritation is the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application.

A.3.1.2 Serious eye damage/eye irritation shall be classified using a tiered approach as detailed in figure A.3.1. Emphasis shall be placed upon existing human data (See A.0.2.6), followed by animal data, followed by other sources of information. Classification results directly when the data satisfy the criteria in this section. In case the criteria cannot be directly applied, classification of a substance or a mixture is made on the basis of the total weight of evidence (See A.0.3.1). This means that all available information bearing on the determination of serious eye damage/eye irritation is considered together, including the results of appropriate scientifically validated *in vitro* tests, relevant animal data, and human data such as epidemiological and clinical studies and well-documented case reports and observations.

A.3.2 Classification criteria for substances using animal test data

A.3.2.1 Irreversible effects on the eye/serious damage to eyes (Category 1)

A single hazard category is provided in Table A.3.1, for substances that have the potential to seriously damage the eyes. Category 1, irreversible effects on the eye, includes the criteria listed below. These observations include animals with grade 4 cornea lesions and other severe reactions (e.g. destruction of cornea) observed at any time during the test, as well as persistent corneal opacity, discoloration of the cornea by a dye substance, adhesion, pannus, and interference with the function of the iris or other effects that impair sight. In this context, persistent lesions are considered those which are not fully reversible within an observation period of normally 21 days. Category 1 also contains substances fulfilling the criteria of corneal opacity ≥ 3 and/or iritis > 1.5 detected in a Draize eye test with rabbits, because severe lesions like these usually do not reverse within a 21-day observation period.

Table A.3.1: Irreversible eye effects

A substance is classified as Serious **Eye Damage Category 1 (irreversible effects on the eye)** when it produces:
(a) at least in one tested animal, effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or
(b) at least in 2 of 3 tested animals, a positive response of:
(i) corneal opacity ≥ 3; and/or
(ii) iritis > 1.5;
calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the substance.

A.3.2.2 Reversible effects on the eye (Category 2)

A single category is provided in Table A.3.2 for substances that have the potential to induce reversible eye irritation.

Table A.3.2: Reversible eye effects

A substance is classified as **Eye irritant Category 2A (irritating to eyes)** when it produces in at least in 2 of 3 tested animals a positive response of:
(i) corneal opacity ≥ 1; and/or
(ii) iritis ≥ 1; and/or
(iii) conjunctival redness ≥ 2; and/or
(iv) conjunctival edema (chemosis) ≥ 2
calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the substance, and which fully reverses within an observation period of normally 21 days.
An eye irritant is considered **mildly irritating to eyes (Category 2B)** when the effects listed above are fully reversible within 7 days of observation.

A.3.2.3 For those chemicals where there is pronounced variability among animal responses, this information may be taken into account in determining the classification.

A.3.3 Classification Criteria for Substances Using Other Data Elements

A.3.3.1 Existing human and animal data should be the first line of analysis, as they give information directly relevant to effects on the eye. Possible skin corrosion shall be evaluated prior to consideration of serious eye damage/eye irritation in order to avoid testing for local effects on eyes with skin corrosive substances. *In vitro* alternatives that have been scientifically validated and accepted shall be used to make classification decisions. Likewise, pH extremes like ≤ 2 and ≥ 11.5, may indicate serious eye damage, especially when associated with significant buffering capacity. Generally, such substances are expected to produce significant effects on the eyes. In the absence of any other information, a mixture/substance is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. However, if consideration of acid/alkaline reserve suggests the substance may not have the potential to cause serious eye damage despite the low or high pH value, then further evaluation may be necessary. In some cases enough information may be available from structurally related compounds to make classification decisions.

A.3.3.2 A tiered approach to the evaluation of initial information shall be used where applicable, recognizing that all elements may not be relevant in certain cases (Figure A.3.1).

A.3.3.3 The tiered approach explains how to organize existing information on a substance and to make a weight-of-evidence decision, where appropriate, about hazard assessment and hazard classification.

A.3.3.4 All the above information that is available on a substance shall be evaluated. Although information might be gained from the evaluation of single parameters within a tier, consideration should be given to the totality of existing information and making an overall weight of evidence determination. This is especially true when there is conflict in information available on some parameters.

Figure A.3.1 Evaluation strategy for serious eye damage and eye irritation
(See also Figure A.2.1)

Step	Parameter	Finding	Conclusion
1a:	Existing human or animal data, eye[1]	Serious Eye Damage	Category 1[2]
		Eye Irritant	Category 2[2]
	No/insufficient data or unknown		
1b:	Existing human or animal data, skin corrosion	Skin corrosive	Category 1[2]
	No/insufficient data or unknown		
1c:	Existing human or animal data, eye[1]	Existing data that show that substance does not cause serious eye damage or eye irritation	Not Classified
	No/insufficient data		
2:	Other, existing skin/eye data in animals[3]	Yes; existing data that show that substance may cause serious eye damage or eye irritation	Category1 or Category 2[2]
	No/insufficient data		
3:	Existing *ex vivo / in vitro* data[4]	Positive: serious eye damage	Category 1[2]
		Positive: eye irritant	Category 2[2]
	No/insufficient data / negative response		
4:	pH-Based assessment (with consideration of buffering capacity of the chemical, or no buffering capacity data)[5]	pH ≤ 2 or ≥11.5	Category 1[2]
	Not a pH extreme, no pH data, or extreme pH with low/no buffering capacity		
5:	Validated structure/activity relationship (SAR) models	Severe damage to eyes	Category 1[2]
		Eye irritant	Category 2[2]
		Skin Corrosive	Category 1[2]
	No/insufficient data		
6:	Consideration of the total weight of evidence[6]	Serious eye damage	Category 1[2]
		Eye irritant	Category 2[2]
	No concern based on consideration of the sum of available data		
7:	**Not Classified**		

Notes to Figure A.3.1:

1 Evidence of existing human or animal data may be derived from single or repeated exposure(s) in occupational, consumer, transportation, or emergency response scenarios; from ethically-conducted human clinical studies; or from purposely-generated data from animal studies conducted according to scientifically validated test methods. At present, there are no internationally accepted test methods for human skin or eye irritation testing.

2 Classify in the appropriate harmonized category, as shown in Tables A.3.1 and A.3.2.

3 Pre-existing animal data should be carefully reviewed to determine if sufficient skin or eye corrosion/irritation evidence is available through other, similar information.

4 Evidence from studies using scientifically validated protocols with isolated human/animal tissues or other, non-tissue-based, though scientifically validated, protocols should be assessed. Examples of, scientifically validated test methods for identifying eye corrosives and severe irritants (i.e., Serious Eye Damage) include OECD TG 437 (Bovine Corneal Opacity and Permeability (BCOP)) and TG 438 (Isolated Chicken Eye). Positive test results from a scientifically validated in vitro test for skin corrosion would likely also lead to a conclusion to classify as causing Serious Eye Damage.

5 Measurement of pH alone may be adequate, but assessment of acid or alkali reserve (buffering capacity) would be preferable.

6 All information that is available on a chemical should be considered and an overall determination made on the total weight of evidence. This is especially true when there

is conflict in information available on some parameters. The weight of evidence including information on skin irritation could lead to classification of eye irritation. It is recognized that not all skin irritants are eye irritants as well. Professional judgment should be exercised in making such a determination.

A.3.4 Classification criteria for mixtures

A.3.4.1 Classification of mixtures when data are available for the complete mixture

A.3.4.1.1 The mixture will be classified using the criteria for substances

A.3.4.1.2 Unlike other hazard classes, there are alternative tests available for skin corrosivity of certain types of chemicals that can give an accurate result for classification purposes, as well as being simple and relatively inexpensive to perform. When considering testing of the mixture, chemical manufacturers are encouraged to use a tiered weight of evidence strategy as included in the criteria for classification of substances for skin corrosion and serious eye damage and eye irritation to help ensure an accurate classification, as well as avoid unnecessary animal testing. In the absence of any other information, a mixture is considered to cause serious eye damage (Eye Category 1) if it has a pH ≤ 2 or ≥ 11.5. However, if consideration of acid/alkaline reserve suggests the substance or mixture may not have the potential to cause serious eye damage despite the low or high pH value, then further evaluation may be necessary.

A.3.4.2 Classification of mixtures when data are not available for the complete mixture: bridging principles

A.3.4.2.1 Where the mixture itself has not been tested to determine its skin corrosivity or potential to cause serious eye damage or eye irritation, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles, as found in paragraph A.0.5 of this Appendix: Dilution, Batching, Concentration of mixtures, Interpolation within one toxicity category, Substantially similar mixtures, and Aerosols.

A.3.4.3 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A.3.4.3.1 For purposes of classifying the eye corrosion/irritation hazards of mixtures in the tiered approach:

The "relevant ingredients" of a mixture are those which are present in concentrations ≥1% (weight/weight for solids, liquids, dusts, mists and vapors and volume/volume for gases.) If the classifier has reason to suspect that an ingredient present at a concentration <1% will affect classification of the mixture for eye corrosion/irritation, that ingredient shall also be considered relevant.

A.3.4.3.2 In general, the approach to classification of mixtures as seriously damaging to the eye or eye irritant when data are available on the ingredients, but not on the mixture as a whole, is based on the theory of additivity, such that each corrosive or irritant ingredient contributes to the overall irritant or corrosive properties of the mixture in proportion to its potency and concentration. A weighting factor of 10 is used for corrosive ingredients when they are present at a concentration below the concentration limit for classification with Category 1, but are at a concentration that will contribute to the classification of the mixture as an irritant. The mixture is classified as seriously damaging to the eye or eye irritant when the sum of the concentrations of such ingredients exceeds a threshold cut-off value/concentration limit.

A.3.4.3.3 Table A.3.3 provides the cut-off value/concentration limits to be used to determine if the mixture should be classified as seriously damaging to the eye or an eye irritant.

A.3.4.3.4 Particular care must be taken when classifying certain types of chemicals such as acids and bases, inorganic salts, aldehydes, phenols, and surfactants. The approach explained in A.3.4.3.1 and A.3.4.3.2 might not work given that many of such substances are corrosive or irritant at concentrations < 1%. For mixtures containing strong acids or bases, the pH should be used as classification criteria (See A.3.4.1) since pH will be a better indicator of serious eye damage than the concentration limits of Table A.3.3. A mixture containing corrosive or irritant ingredients that cannot be classified based on the additivity approach applied in Table A.3.3 due to chemical characteristics that make this approach unworkable, should be classified as Eye Category 1 if it contains ≥ 1% of a corrosive ingredient and as Eye Category 2 when it contains ≥ 3% of an irritant ingredient. Classification of mixtures with ingredients for which the approach in Table A.3.3 does not apply is summarized in Table A.3.4.

A.3.4.3.5 On occasion, reliable data may show that the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic cut-off values/concentration limits mentioned in Tables A.3.3 and A.3.4. In these cases the mixture could be classified according to those data (See also A.0.4.3 *Use of cut-off values/concentration limits*). On occasion, when it is expected that the skin corrosion/irritation or the reversible/irreversible eye effects of an ingredient will not be evident when present at a level above the generic concentration/cut-off levels mentioned in Tables A.3.3 and A.3.4, testing of the mixture may be considered. In those cases, the tiered weight of evidence strategy should be applied as referred to in section A.3.3, Figure A.3.1 and explained in detail in this chapter.

A.3.4.3.6 If there are data showing that (an) ingredient(s) may be corrosive or irritant at a concentration of < 1% (corrosive) or < 3% (irritant), the mixture should be classified accordingly (See also paragraph A.0.4.3, *Use of cut-off values/concentration limits*).

Table A.3.3: Concentration of ingredients of a mixture classified as Skin Category 1 and/or Eye Category 1 or 2 that would trigger classification of the mixtures as hazardous to the eye

Sum of ingredients classified as	Concentration triggering classification of a mixture as	
	Irreversible eye effects	Reversible eye effects
	Category 1	Category 2
Eye or Skin Category 1	≥ 3%	≥ 1% but < 3%
Eye Category 2		≥ 10%
(10 x Eye Category 1) + Eye Category 2		≥ 10%
Skin Category 1 + Eye Category 1	≥ 3%	≥ 1% but < 3%
10 x (Skin Category 1 + Eye Category 1) + Eye Category 2		≥ 10%

Note: A mixture may be classified as Eye Category 2B in cases when all relevant ingredients are classified as Eye Category 2B.

Table A.3.4: Concentration of ingredients of a mixture for which the additivity approach does not apply, that would trigger classification of the mixture as hazardous to the eye

Ingredient	Concentration	Mixture classified as: Eye
Acid with pH ≤ 2	≥ 1%	Category 1

Base with pH ≥ 11.5	≥ 1%	Category 1
Other corrosive (Category 1) ingredients for which additivity does not apply	≥ 1%	Category 1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	≥ 3%	Category 2

A.4 RESPIRATORY OR SKIN SENSITIZATION

A.4.1 Definitions and general considerations

A.4.1.1 *Respiratory sensitizer* means a chemical that will lead to hypersensitivity of the airways following inhalation of the chemical.

Skin sensitizer means a chemical that will lead to an allergic response following skin contact.

A.4.1.2 For the purpose of this chapter, sensitization includes two phases: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e., production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen.

A.4.1.3 For respiratory sensitization, the pattern of induction followed by elicitation phases is shared in common with skin sensitization. For skin sensitization, an induction phase is required in which the immune system learns to react; clinical symptoms can then arise when subsequent exposure is sufficient to elicit a visible skin reaction (elicitation phase). As a consequence, predictive tests usually follow this pattern in which there is an induction phase, the response to which is measured by a standardized elicitation phase, typically involving a patch test. The local lymph node assay is the exception, directly measuring the induction response. Evidence of skin sensitization in humans normally is assessed by a diagnostic patch test.

A.4.1.4 Usually, for both skin and respiratory sensitization, lower levels are necessary for elicitation than are required for induction.

A.4.1.5 The hazard class "respiratory or skin sensitization" is differentiated into:

(a) Respiratory sensitization; and

(b) Skin sensitization

A.4.2 Classification criteria for substances

A.4.2.1 Respiratory sensitizers

A.4.2.1.1 Hazard categories

A.4.2.1.1.1 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for respiratory sensitizers. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table A.4.1 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals.

A.4.2.1.1.2 Where data are not sufficient for sub-categorization, respiratory sensitizers shall be classified in Category 1.

Table A.4.1: Hazard category and sub-categories for respiratory sensitizers

Category 1:	**Respiratory sensitizer**
	A substance is classified as a respiratory sensitizer (a) if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity and/or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitization rate in humans based on animal or other tests.1 Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitization rate in humans based on animal or other tests.1 Severity of reaction may also be considered.

A.4.2.1.2 Human evidence

A.4.2.1.2.1 Evidence that a substance can lead to specific respiratory hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

A.4.2.1.2.2 When considering the human evidence, it is necessary that in addition to the evidence from the cases, the following be taken into account:

(a) the size of the population exposed;

(b) the extent of exposure.

A.4.2.1.2.3 The evidence referred to above could be:

(a) clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

(i) in vivo immunological test (e.g., skin prick test);

(ii) in vitro immunological test (e.g., serological analysis);

(iii) studies that may indicate other specific hypersensitivity reactions where immunological mechanisms of action have not been proven, e.g., repeated low-level irritation, pharmacologically mediated effects;

(iv) a chemical structure related to substances known to cause respiratory hypersensitivity;

(b) data from positive bronchial challenge tests with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

A.4.2.1.2.4 Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood and smoking history.

A.4.2.1.2.5 The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is, however, recognized that in practice many of the examinations listed above will already have been carried out.

A.4.2.1.3 Animal studies

A.4.2.1.3.1 Data from appropriate animal studies which may be indicative of the potential of a substance to cause sensitization by inhalation in humans may include:

(a) measurements of Immunoglobulin E (IgE) and other specific immunological parameters, for example in mice

(b) specific pulmonary responses in guinea pigs.

A.4.2.2 Skin sensitizers

A.4.2.2.1 Hazard categories

A.4.2.2.1.1 Effects seen in either humans or animals will normally justify classification in a weight of evidence approach for skin sensitizers. Substances may be allocated to one of the two sub-categories 1A or 1B using a weight of evidence approach in accordance with the criteria given in Table A.4.2 and on the basis of reliable and good quality evidence from human cases or epidemiological studies and/or observations from appropriate studies in experimental animals according to the guidance values provided in A.4.2.2.2.1 and A.4.2.2.3.2 for sub-category 1A and in A.4.2.2.2.2 and A.4.2.2.3.3 for sub-category 1B.

A.4.2.2.1.2 Where data are not sufficient for sub-categorization, skin sensitizers shall be classified in Category 1.

Table A.4.2: Hazard category and sub-categories for skin sensitizers

Category 1:	**Skin sensitizer**
	A substance is classified as a skin sensitizer (a) if there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons, or (b) if there are positive results from an appropriate animal test.
Sub-category 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitization in humans. Severity of reaction may also be considered.
Sub-category 1B:	Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitization in humans. Severity of reaction may also be considered.

A.4.2.2.2 Human evidence

A.4.2.2.2.1 Human evidence for sub-category 1A may include:

(a) positive responses at ≤ 500 μg/cm^2 (Human Repeat Insult Patch Test (HRIPT), Human Maximization Test (HMT) – induction threshold);

(b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;

(c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

A.4.2.2.2.2 Human evidence for sub-category 1B may include:

(a) positive responses at > 500 μg/cm^2 (HRIPT, HMT – induction threshold);

(b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;

(c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

A.4.2.2.3 Animal studies

A.4.2.2.3.1 For Category 1, when an adjuvant type test method for skin sensitization is used, a response of at least 30% of the animals is considered as positive. For a non-adjuvant Guinea pig test method a response of at least 15% of the animals is considered positive. For Category 1, a stimulation index of three or more is considered a positive response in the local lymph node assay.

A.4.2.2.3.2 Animal test results for sub-category 1A can include data with values indicated in Table A.4.3 below:

Table A.4.3: Animal test results for sub-category 1A

Assay	**Criteria**
Local lymph node assay	EC3 value ≤ 2%
Guinea pig maximization test	≥ 30% responding at ≤ 0.1% intradermal induction dose **or** ≥ 60% responding at > 0.1% to ≤ 1% intradermal induction dose

Buehler assay	≥ 15% responding at ≤ 0.2% topical induction dose **or** ≥ 60% responding at > 0.2% to ≤ 20% topical induction dose

Note: EC3 refers to the estimated concentration of test chemical required to induce a stimulation index of 3 in the local lymph node assay.

A.4.2.2.3.3 Animal test results for sub-category 1B can include data with values indicated in Table A.4.4 below:

Table A.4.4: Animal test results for sub-category 1B

Assay	Criteria
Local lymph node assay	EC3 value > 2%
Guinea pig maximization test	≥ 30% to < 60% responding at > 0.1% to ≤ 1% intradermal induction dose or ≥ 30% responding at > 1% intradermal induction dose
Buehler assay	≥ 15% to < 60% responding at > 0.2% to ≤ 20% topical induction dose or ≥ 15% responding at > 20% topical induction dose

Note: EC3 refers to the estimated concentration of test chemical required to induce a stimulation index of 3 in the local lymph node assay.

A.4.2.2.4 Specific considerations

A.4.2.2.4.1 For classification of a substance, evidence shall include one or more of the following using a weight of evidence approach:

(a) Positive data from patch testing, normally obtained in more than one dermatology clinic;

(b) Epidemiological studies showing allergic contact dermatitis caused by the substance. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small;

(c) Positive data from appropriate animal studies;

(d) Positive data from experimental studies in man (See paragraph A.0.2.6 of this Appendix);

(e) Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic;

(f) Severity of reaction.

A.4.2.2.4.2 Evidence from animal studies is usually much more reliable than evidence from human exposure. However, in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis. Normally, human data are not generated in controlled experiments with volunteers for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests. Consequently, positive human data on skin sensitization are usually derived from case-control or other, less defined studies. Evaluation of human data must, therefore, be carried out with caution as the frequency of cases reflect, in addition to the inherent properties of the substances, factors such as the exposure situation, bioavailability, individual predisposition and preventive measures taken. Negative human data should not normally be used to negate positive results from animal studies. For both animal and human data, consideration should be given to the impact of vehicle.

A.4.2.2.4.3 If none of the above-mentioned conditions are met, the substance need not be classified as a skin sensitizer. However, a combination of two or more indicators of skin sensitization, as listed below, may alter the decision. This shall be considered on a case-by-case basis.

(a) Isolated episodes of allergic contact dermatitis;

(b) Epidemiological studies of limited power, e.g., where chance, bias or confounders have not been ruled out fully with reasonable confidence;

(c) Data from animal tests, performed according to existing guidelines, which do not meet the criteria for a positive result described in A.4.2.2.3, but which are sufficiently close to the limit to be considered significant;

(d) Positive data from non-standard methods;

(e) Positive results from close structural analogues.

A.4.2.2.4.4 Immunological contact urticaria

A.4.2.2.4.4.1 Substances meeting the criteria for classification as respiratory sensitizers may, in addition, cause immunological contact urticaria. Consideration shall be given to classifying these substances as skin sensitizers.

A.4.2.2.4.4.2 Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitizers shall be considered for classification as skin sensitizers.

A.4.2.2.4.4.3 There is no recognized animal model available to identify substances which cause immunological contact urticaria. Therefore, classification will normally be based on human evidence, similar to that for skin sensitization.

A.4.3 Classification criteria for mixtures

A.4.3.1 Classification of mixtures when data are available for the complete mixture

When reliable and good quality evidence, as described in the criteria for substances, from human experience or appropriate studies in experimental animals, is available for the mixture, then the mixture shall be classified by weight of evidence evaluation of these data. Care must be exercised in evaluating data on mixtures that the dose used does not render the results inconclusive.

A.4.3.2 Classification of mixtures when data are not available for the complete mixture: bridging principles

A.4.3.2.1 Where the mixture itself has not been tested to determine its sensitizing properties, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following agreed bridging principles as found in

paragraph A.0.5 of this Appendix: Dilution, Batching, Concentration of mixtures, Interpolation, Substantially similar mixtures, and Aerosols.

A.4.3.3 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

The mixture shall be classified as a respiratory or skin sensitizer when at least one ingredient has been classified as a respiratory or skin sensitizer and is present at or above the appropriate cut-off value/concentration limit for the specific endpoint as shown in Table A.4.5.

Table A.4.5: Cut-off values/concentration limits of ingredients of a mixture classified as either respiratory sensitizers or skin sensitizers that would trigger classification of the mixture

Ingredient classified as:	Cut-off values/concentration limits triggering classification of a mixture as:		
	Respiratory Sensitizer Category 1		Skin Sensitizer Category 1
	Solid/Liquid	Gas	All physical states
Respiratory Sensitizer Category 1	≥ 0.1%	≥ 0.1%	
Respiratory Sensitizer Sub-category 1A	≥ 0.1%	≥ 0.1%	
Respiratory Sensitizer Sub-category 1B	≥ 0.1%	≥ 0.2%	
Skin Sensitizer Category 1			≥ 0.1%
Skin Sensitizer Sub-category 1A			≥ 0.1%
Skin Sensitizer Sub-category 1B			≥ 1.0%

A.5 GERM CELL MUTAGENICITY

A.5.1 Definitions and general considerations

A.5.1.1 A *mutation* is defined as a permanent change in the amount or structure of the genetic material in a cell. The term *mutation* applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including, for example, specific base pair changes and chromosomal translocations). The term *mutagenic* and *mutagen* will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

A.5.1.2 The more general terms *genotoxic* and *genotoxicity* apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

A.5.1.3 This hazard class is primarily concerned with chemicals that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, mutagenicity/genotoxicity tests *in vitro* and in mammalian somatic cells *in vivo* are also considered in classifying substances and mixtures within this hazard class.

A.5.2 Classification criteria for substances

A.5.2.1 The classification system provides for two different categories of germ cell mutagens to accommodate the weight of evidence available. The two-category system is described in the Figure A.5.1.

Figure A.5.1: Hazard categories for germ cell mutagens

CATEGORY 1:	**Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans**
Category 1A:	**Substances known to induce heritable mutations in germ cells of humans** Positive evidence from human epidemiological studies.
Category 1B:	**Substances which should be regarded as if they induce heritable mutations in the germ cells of humans** (a) Positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or (b) Positive result(s) from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. This supporting evidence may, for example, be derived from mutagenicity/genotoxicity tests in germ cells *in vivo*, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or (c) Positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
CATEGORY 2:	**Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans** Positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from: (a) Somatic cell mutagenicity tests *in vivo*, in mammals; or (b) Other in vivo somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays. *Note: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, should be considered for classification as Category 2 mutagens.*

A.5.2.2 Specific considerations for classification of substances as germ cell mutagens:

A.5.2.2.1 To arrive at a classification, test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed

animals. Mutagenic and/or genotoxic effects determined in *in vitro* tests shall also be considered.

A.5.2.2.2 The system is hazard based, classifying chemicals on the basis of their intrinsic ability to induce mutations in germ cells. The scheme is, therefore, not meant for the (quantitative) risk assessment of chemical substances.

A.5.2.2.3 Classification for heritable effects in human germ cells is made on the basis of scientifically validated tests. Evaluation of the test results shall be done using expert judgment and all the available evidence shall be weighed for classification.

A.5.2.2.4 The classification of substances shall be based on the total weight of evidence available, using expert judgment. In those instances where a single well-conducted test is used for classification, it shall provide clear and unambiguously positive results. The relevance of the route of exposure used in the study of the substance compared to the route of human exposure should also be taken into account.

A.5.3 Classification criteria for mixtures

A.5.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A.5.3.1.1 Classification of mixtures shall be based on the available test data for the individual ingredients of the mixture using cut-off values/concentration limits for the ingredients classified as germ cell mutagens.

A.5.3.1.2 The mixture will be classified as a mutagen when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 mutagen and is present at or above the appropriate cut-off value/concentration limit as shown in Table A.5.1 below for Category 1 and 2 respectively.

Table A.5.1: Cut-off values/concentration limits of ingredients of a mixture classified as germ cell mutagens that would trigger classification of the mixture

Ingredient classified as:	Cut-off/concentration limits triggering classification of a mixture as:	
	Category 1 mutagen	Category 2 mutagen
Category 1A/B mutagen	≥ 0.1 %	-
Category 2 mutagen	-	≥ 1.0 %

Note: The cut-off values/concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).

A.5.3.2 Classification of mixtures when data are available for the mixture itself

The classification may be modified on a case-by-case basis based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g. statistical analysis, test sensitivity) of germ cell mutagenicity test systems.

A.5.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

A.5.3.3.1 Where the mixture itself has not been tested to determine its germ cell mutagenicity hazard, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution, Batching, and Substantially similar mixtures.

A.5.4 Examples of scientifically validated test methods:

A.5.4.1 Examples of *in vivo* heritable germ cell mutagenicity tests are:

(a) Rodent dominant lethal mutation test (OECD 478)

(b) Mouse heritable translocation assay (OECD 485)

(c) Mouse specific locus test

A.5.4.2 Examples of *in vivo* somatic cell mutagenicity tests are:

(a) Mammalian bone marrow chromosome aberration test (OECD 475)

(b) Mouse spot test (OECD 484)

(c) Mammalian erythrocyte micronucleus test (OECD 474)

A.5.4.3 Examples of mutagenicity/genotoxicity tests in germ cells are:

(a) Mutagenicity tests:

(i) Mammalian spermatogonial chromosome aberration test (OECD 483)

(ii) Spermatid micronucleus assay

(b) Genotoxicity tests:

(i) Sister chromatid exchange analysis in spermatogonia

(ii) Unscheduled DNA synthesis test (UDS) in testicular cells

A.5.4.4 Examples of genotoxicity tests in somatic cells are:

(a) Liver Unscheduled DNA Synthesis (UDS) *in vivo* (OECD 486)

(b) Mammalian bone marrow Sister Chromatid Exchanges (SCE)

A.5.4.5 Examples of *in vitro* mutagenicity tests are:

(a) *In vitro* mammalian chromosome aberration test (OECD 473)

(b) *In vitro* mammalian cell gene mutation test (OECD 476)

(c) Bacterial reverse mutation tests (OECD 471)

A.5.4.6 As new, scientifically validated tests arise, these may also be used in the total weight of evidence to be considered.

A.6 CARCINOGENICITY

A.6.1 Definitions

Carcinogen means a substance or a mixture of substances which induce cancer or increase its incidence. Substances and mixtures which have induced benign and malignant tumors in well-performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumor formation is not relevant for humans.

Classification of a substance or mixture as posing a carcinogenic hazard is based on its inherent properties and does not provide information on the level of the human cancer risk which the use of the substance or mixture may represent.

A.6.2 Classification criteria for substances

A.6.2.1 For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional weight of evidence considerations. In certain instances, route-specific classification may be warranted.

Figure A.6.1: Hazard categories for carcinogens

CATEGORY 1:	**Known or presumed human carcinogens** The classification of a substance as a Category 1 carcinogen is done on the basis of epidemiological and/or animal data. This classification is further distinguished on the basis of whether the evidence for classification is largely from human data (Category 1A) or from animal data (Category 1B):
Category 1A:	**Known to have carcinogenic potential for humans. Classification in this category is largely based on human evidence.**
Category 1B:	**Presumed to have carcinogenic potential for humans. Classification in this category is largely based on animal evidence.** The classification of a substance in Category 1A and 1B is based on strength of evidence together with weight of evidence considerations (See paragraph A.6.2.5). Such evidence may be derived from: - human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or - animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgment may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcino¬genicity in experimental animals.
CATEGORY 2:	**Suspected human carcinogens** The classification of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or B. This classification is based on strength of evidence together with weight of evidence considerations (See paragraph A.6.2.5). Such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.
Other considerations:	Where the weight of evidence for the carcinogenicity of a substance does not meet the above criteria, any positive study conducted in accordance with established scientific principles, and which reports statistically significant findings regarding the carcinogenic potential of the substance, must be noted on the safety data sheet.

A.6.2.2 Classification as a carcinogen is made on the basis of evidence from reliable and acceptable methods, and is intended to be used for substances which have an intrinsic property to produce such toxic effects. The evaluations are to be based on all existing data, peer-reviewed published studies and additional data accepted by regulatory agencies.

A.6.2.3 *Carcinogen classification* is a one-step, criterion-based process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.

A.6.2.4 *Strength of evidence* involves the enumeration of tumors in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the agent and an increased incidence of tumors. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. (Guidance on consideration of important factors in the classification of carcinogenicity and a more detailed description of the terms "limited" and "sufficient" have been developed by the International Agency for Research on Cancer (IARC) and are provided in non-mandatory Appendix F.)

A.6.2.5 *Weight of evidence*: Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors should be considered that influence the overall likelihood that an agent may pose a carcinogenic hazard in humans. The full list of factors that influence this determination is very lengthy, but some of the important ones are considered here.

A.6.2.5.1 These factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The rela¬tive emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumor findings and the other factors in a case-by-case manner.

A.6.2.5.2 Some important factors which may be taken into consideration, when assessing the overall level of concern are:

(a) Tumor type and background incidence;

(b) Multisite responses;

(c) Progression of lesions to malignancy;

(d) Reduced tumor latency;

Additional factors which may increase or decrease the level of concern include:

(e) Whether responses are in single or both sexes;

(f) Whether responses are in a single species or several species;

(g) Structural similarity or not to a substance(s) for which there is good evidence of carcinogenicity;

(h) Routes of exposure;

(i) Comparison of absorption, distribution, metabolism and excretion between test animals and humans;

(j) The possibility of a confounding effect of excessive toxicity at test doses; and,

(k) Mode of action and its relevance for humans, such as mutagenicity, cytotoxicity with growth stimulation, mitogenesis, immunosuppression.

Mutagenicity: It is recognized that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity *in vivo* may indicate that a substance has a potential for carcinogenic effects.

A.6.2.5.3 A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B, or Category 2 based on tumor data from a structural analogue together with substantial support from consi¬deration of other important factors such as formation of common significant metabolites, e.g., for benzidine congener dyes.

A.6.2.5.4 The classification should also take into consideration whether or not the substance is absorbed by a given route(s); or whether there are only local tumors at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

A.6.2.5.5 It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e., structure activity relationship, is taken into consideration when undertaking classification.

A.6.3 Classification criteria for mixtures

A.6.3.1 The mixture shall be classified as a carcinogen when at least one ingredient has been classified as a Category 1 or Category 2 carcinogen and is present at or above the appropriate cut-off value/concentration limit as shown in Table A.6.1.

Table A.6.1: Cut-off values/concentration limits of ingredients of a mixture classified as carcinogen that would trigger classification of the mixture

Ingredient classified as:	Category 1 carcinogen	Category 2 carcinogen
Category 1 carcinogen	≥ 0.1 %	
Category 2 carcinogen		≥ 0.1% (note 1)

Note: If a Category 2 carcinogen ingredient is present in the mixture at a concentration between 0.1% and 1%, information is required on the SDS for a product. However, a label warning is optional. If a Category 2 carcinogen ingredient is present in the mixture at a concentration of ≥ 1%, both an SDS and a label is required and the information must be included on each.

A.6.3.2 Classification of mixtures when data are available for the complete mixture

A mixture may be classified based on the available test data for the mixture as a whole. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g., statistical analysis, test sensitivity) of carcinogenicity test systems.

A.6.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

Where the mixture itself has not been tested to determine its carcinogenic hazard, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data will be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution; Batching; and Substantially similar mixtures.

A.6.4 Classification of carcinogenicity

A.6.4.1 Chemical manufacturers, importers and employers evaluating chemicals may treat the following sources as establishing that a substance is a carcinogen or potential carcinogen for hazard communication purposes in lieu of applying the criteria described herein:

A.6.4.1.1 National Toxicology Program (NTP), "Report on Carcinogens" (latest edition);

A.6.4.1.2 International Agency for Research on Cancer (IARC) "Monographs on the Evaluation of Carcinogenic Risks to Humans" (latest editions)

A.6.4.2 Where OSHA has included cancer as a health hazard to be considered by classifiers for a chemical covered by 29 CFR part 1910, Subpart Z, Toxic and Hazardous Substances, chemical manufacturers, importers, and employers shall classify the chemical as a carcinogen.

A.7 REPRODUCTIVE TOXICITY

A.7.1 Definitions and general considerations

A.7.1.1 *Reproductive toxicity* includes *adverse effects on sexual function and fertility* in adult males and females, as well as *adverse effects on development of the offspring.* Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, chemicals with these effects shall be classified as reproductive toxicants.

For classification purposes, the known induction of genetically based inheritable effects in the offspring is addressed in *Germ cell mutagenicity* (See A.5).

A.7.1.2 *Adverse effects on sexual function and fertility* means any effect of chemicals that interferes with reproductive ability or sexual capacity. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

A.7.1.3 *Adverse effects on development of the offspring* means any effect of chemicals which interferes with normal development of the conceptus either before or after birth, which is induced during pregnancy or results from parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth and functional deficiency.

A.7.1.4 Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately (See A.7.2.1).

A.7.2 Classification criteria for substances

A.7.2.1 For the purpose of classification for reproductive toxicity, substances shall be classified in one of two categories in accordance with Figure A.7.1(a). Effects on sexual function and fertility, and on development, shall be considered. In addition, effects on or via lactation shall be classified in a separate hazard category in accordance with Figure A.7.1(b).

Figure A.7.1(a): Hazard categories for reproductive toxicants

CATEGORY 1:	**Known or presumed human reproductive toxicant** Substance shall be classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
Category 1A:	**Known human reproductive toxicant** The classification of a substance in this category is largely based on evidence from humans.
Category 1B:	**Presumed human reproductive toxicant** The classification of a substance in this category is largely based on evidence from experimental animals. Data from animal studies shall provide sufficient evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.
CATEGORY 2:	**Suspected human reproductive toxicant** Substances shall be classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects, and where the evidence is not sufficiently convincing to place the substance in Category 1. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this, Category 2 would be the more appropriate classification.

Figure A.7.1(b): Hazard category for effects on or via lactation

EFFECTS ON OR VIA LACTATION

Effects on or via lactation shall be classified in a separate single category. Chemicals that are absorbed by women and have been shown to interfere with lactation or that may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified to indicate this property hazardous to breastfed babies. This classification shall be assigned on the basis of:

(a) absorption, metabolism, distribution and excretion studies that indicate the likelihood the substance would be present in potentially toxic levels in breast milk; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) human evidence indicating a hazard to babies during the lactation period.

A.7.2.2 Basis of classification

A.7.2.2.1 Classification is made on the basis of the criteria, outlined above, an assessment of the total weight of evidence, and the use of expert judgment. Classification as a reproductive toxicant is intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction and substances should not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects.

A.7.2.2.2 In the evaluation of toxic effects on the developing offspring, it is important to consider the possible influence of maternal toxicity.

A.7.2.2.3 For human evidence to provide the primary basis for a Category 1A classification there must be reliable evidence of an adverse effect on reproduction in humans. Evidence used for classification shall be from well conducted epidemiological studies, if available, which include the use of appropriate controls, balanced assessment, and due consideration of bias or confounding factors. Less rigorous data from studies in humans may be sufficient for a Category 1A classification if supplemented with adequate data from studies in experimental animals, but classification in Category 1B may also be considered.

A.7.2.3 Weight of evidence

A.7.2.3.1 Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence using expert judgment. This means that all available information that bears on the determination of reproductive toxicity is considered together. Included is information such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs. Evaluation of substances chemically related to the material under study may also be included, particularly when information on the material is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, level of statistical significance for intergroup differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are considered together in a weight of evidence determination. However, a single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (See also A.7.2.2.3).

A.7.2.3.2 Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may provide relevant information, which could reduce or increase concerns about the hazard to human health. If it is conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a chemical which produces an adverse effect on reproduction in experimental animals should not be classified.

A.7.2.3.3 In some reproductive toxicity studies in experimental animals the only effects recorded may be considered of low or minimal toxicological significance and classification may not necessarily be the outcome. These effects include, for example, small changes in semen parameters or in the incidence of spontaneous defects in the fetus, small changes in the proportions of common fetal variants such as are observed in skeletal examinations, or in fetal weights, or small differences in postnatal developmental assessments.

A.7.2.3.4 Data from animal studies shall provide sufficient evidence of specific reproductive toxicity in the absence of other systemic toxic effects. However, if developmental toxicity occurs together with other toxic effects in the dam (mother), the potential influence of the generalized adverse effects should be assessed to the extent possible. The preferred approach is to consider adverse effects in the embryo/fetus first, and then evaluate maternal toxicity, along with any other factors which are likely to have influenced these effects, as part of the weight of evidence. In general, developmental effects that are observed at maternally toxic doses should not be automatically discounted. Discounting developmental effects that are observed at maternally toxic doses can only be done on a case-by-case basis when a causal relationship is established or refuted.

A.7.2.3.5 If appropriate information is available it is important to try to determine whether developmental toxicity is due to a specific maternally mediated mechanism or to a non-specific secondary mechanism, like maternal stress and the disruption of homeostasis. Generally, the presence of maternal toxicity should not be used to negate findings of embryo/fetal effects, unless it can be clearly demonstrated that the effects are secondary non-specific effects. This is especially the case when the effects in the offspring are significant, e.g., irreversible effects such as structural malformations. In some situations it is reasonable to assume that reproductive toxicity is due to a secondary consequence of maternal toxicity and discount the effects, for example if the chemical is so toxic that dams fail to thrive and there is severe inanition; they are incapable of nursing pups; or they are prostrate or dying.

A.7.2.4 Maternal toxicity

A.7.2.4.1 Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. So, in the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgment and a weight of evidence approach, using all available studies, shall be used to determine the degree of influence to be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/fetus shall be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification.

A.7.2.4.2 Based on pragmatic observation, it is believed that maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed fetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited numbers of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g., irreversible effects such as structural malformations, embryo/fetal lethality, or significant post-natal functional deficiencies.

A.7.2.4.3 Classification shall not automatically be discounted for chemicals that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a chemical is so toxic that maternal death or severe inanition results, or the dams (mothers) are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification is not necessarily the outcome in the case of minor developmental changes, e.g., a small reduction in fetal/pup body weight or retardation of ossification when seen in association with maternal toxicity.

A.7.2.4.4 Some of the endpoints used to assess maternal toxicity are provided below. Data on these endpoints, if available, shall be evaluated in light of their statistical or biological significance and dose-response relationship.

(a) Maternal mortality: An increased incidence of mortality among the treated dams over the controls shall be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10% is considered excessive and the data for that dose level shall not normally be considered to need further evaluation.

(b) Mating index (Number of animals with seminal plugs or sperm/Number of mated x 100)

(c) Fertility index (Number of animals with implants/Number of matings x 100)

(d) Gestation length (If allowed to deliver)

(e) Body weight and body weight change: Consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight shall be included in the evaluation of maternal toxicity whenever such data are available. The calculation of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the fetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be a useful indicator of maternal toxicity because of normal fluctuations in body weight during pregnancy.

(f) Food and water consumption (if relevant): The observation of a significant decrease in the average food or water consumption in treated dams (mothers) compared to the control group may be useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption must be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity or more simply, unpalatability of the test material in feed or water.

(g) Clinical evaluations (including clinical signs, markers, and hematology and clinical chemistry studies): The observation of increased incidence of significant clinical signs of toxicity in treated dams (mothers) relative to the control group is useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs shall be reported in the study. Clinical signs of maternal intoxication

include, but are not limited to: coma, prostration, hyperactivity, loss of righting reflex, ataxia, or labored breathing.

(h) Post-mortem data: Increased incidence and/or severity of post-mortem findings may be indicative of maternal toxicity. This can include gross or microscopic pathological findings or organ weight data, including absolute organ weight, organ to body weight ratio, or organ to brain weight ratio. When supported by findings of adverse histopathological effects in the affected organ(s), the observation of a significant change in the average weight of suspected target organ(s) of treated dams (mothers), compared to those in the control group, may be considered evidence of maternal toxicity.

A.7.2.5 Animal and experimental data

A.7.2.5.1 A number of scientifically validated test methods are available, including methods for developmental toxicity testing (e.g., OECD Test Guideline 414, ICH Guideline S5A, 1993), methods for peri- and post-natal toxicity testing (e.g., ICH S5B, 1995), and methods for one or two-generation toxicity testing (e.g., OECD Test Guidelines 415, 416)

A.7.2.5.2 Results obtained from screening tests (e.g., OECD Guidelines 421 - Reproduction/ Developmental Toxicity Screening Test, and 422 - Combined Repeated Dose Toxicity Study with Reproduction/Development Toxicity Screening Test) can also be used to justify classification, although the quality of this evidence is less reliable than that obtained through full studies.

A.7.2.5.3 Adverse effects or changes, seen in short- or long-term repeated dose toxicity studies, which are judged likely to impair reproductive function and which occur in the absence of significant generalized toxicity, may be used as a basis for classification, e.g., histopathological changes in the gonads.

A.7.2.5.4 Evidence from *in vitro* assays, or non-mammalian tests, and from analogous substances using structure-activity relationship (SAR), can contribute to the procedure for classification. In all cases of this nature, expert judgment must be used to assess the adequacy of the data. Inadequate data shall not be used as a primary support for classification.

A.7.2.5.5 It is preferable that animal studies are conducted using appropriate routes of administration which relate to the potential route of human exposure. However, in practice, reproductive toxicity studies are commonly conducted using the oral route, and such studies will normally be suitable for evaluating the hazardous properties of the substance with respect to reproductive toxicity. However, if it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

A.7.2.5.6 Studies involving routes of administration such as intravenous or intraperitoneal injection, which may result in exposure of the reproductive organs to unrealistically high levels of the test substance, or elicit local damage to the reproductive organs, e.g., by irritation, must be interpreted with extreme caution and on their own are not normally the basis for classification.

A.7.2.5.7 There is general agreement about the concept of a limit dose, above which the production of an adverse effect may be considered to be outside the criteria which lead to classification. Some test guidelines specify a limit dose, other test guidelines qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure would not be achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

A.7.2.5.8 In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) do not normally lead to classification, unless other information is available, for example, toxicokinetics information indicating that humans may be more susceptible than animals, to suggest that classification is appropriate.

A.7.2.5.9 However, specification of the actual "limit dose" will depend upon the test method that has been employed to provide the test results.

A.7.3 Classification criteria for mixtures

A.7.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A.7.3.1.1 The mixture shall be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1 or Category 2 reproductive toxicant and is present at or above the appropriate cut-off value/concentration limit specified in Table A.7.1 for Category 1 and 2, respectively.

A.7.3.1.2 The mixture shall be classified for effects on or via lactation when at least one ingredient has been classified for effects on or via lactation and is present at or above the appropriate cut-off value/concentration limit specified in Table A.7.1 for the additional category for effects on or via lactation.

Table A.7.1: Cut-off values/concentration limits of ingredients of a mixture classified as reproductive toxicants or for effects on or via lactation that trigger classification of the mixture

Ingredients classified as:	Cut-off values/concentration limits triggering classification of a mixture as:		
	Category 1 reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via lactation
Category 1 reproductive toxicant	≥ 0.1%		
Category 2 reproductive toxicant		≥ 0.1%	
Additional category for effects on or via lactation			≥ 0.1%

A.7.3.2 Classification of mixtures when data are available for the complete mixture

Available test data for the mixture as a whole may be used for classification on a case-by-case basis. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (e.g., statistical analysis, test sensitivity) of reproduction test systems.

A.7.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

A.7.3.3.1 Where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data shall be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution, Batching, and Substantially similar mixtures.

A.8 SPECIFIC TARGET ORGAN TOXICITY SINGLE EXPOSURE

A.8.1 Definitions and general considerations

A.8.1.1 *Specific target organ toxicity - single exposure, (STOT-SE)* means specific, non-lethal target organ toxicity arising from a single exposure to a chemical. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in A.1 to A.7 and A.10 of this Appendix are included. Specific target organ toxicity following repeated exposure is classified in accordance with *SPECIFIC TARGET ORGAN TOXICITY – REPEATED EXPOSURE* (A.9 of this Appendix) and is therefore not included here.

A.8.1.2 Classification identifies the chemical as being a specific target organ toxicant and, as such, it presents a potential for adverse health effects in people who are exposed to it.

A.8.1.3 The adverse health effects produced by a single exposure include consistent and identifiable toxic effects in humans; or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or hematology of the organism, and these changes are relevant for human health. Human data is the primary source of evidence for this hazard class.

A.8.1.4 Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs.

A.8.1.5 Specific target organ toxicity can occur by any route that is relevant for humans, i.e., principally oral, dermal or inhalation.

A.8.1.6 The classification criteria for specific organ systemic toxicity single exposure are organized as criteria for substances Categories 1 and 2 (See A.8.2.1), criteria for substances Category 3 (See A.8.2.2) and criteria for mixtures (See A.8.3). See also Figure A.8.1.

A.8.2 Classification criteria for substances

A.8.2.1 Substances of Category 1 and Category 2

A.8.2.1.1 Substances shall be classified for immediate or delayed effects separately, by the use of expert judgment on the basis of the weight of all evidence available, including the use of recommended guidance values (See A.8.2.1.9). Substances shall then be classified in Category 1 or 2, depending upon the nature and severity of the effect(s) observed, in accordance with Figure A.8.1.

Figure A.8.1: Hazard categories for specific target organ toxicity following single exposure

CATEGORY 1:	**Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following single exposure** Substances are classified in Category 1 for STOT-SE on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (See A.8.2.1.9) to be used as part of weight-of-evidence evaluation.
CATEGORY 2:	**Substances that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to be harmful to human health following single exposure** Substances are classified in Category 2 for STOT-SE on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (See A.8.2.1.9) in order to help in classification. In exceptional cases, human evidence can also be used to place a substance in Category 2 (See A.8.2.1.6).
CATEGORY 3:	**Transient target organ effects** There are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. This category only includes narcotic effects and respiratory tract irritation. Substances are classified specifically for these effects as discussed in A.8.2.2.
Note: The primary target organ/system shall be identified where possible, and where this is not possible, the substance shall be identified as a general toxicant. The data shall be evaluated and, where possible, shall not include secondary effects (e.g., a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).	

A.8.2.1.2 The relevant route(s) of exposure by which the classified substance produces damage shall be identified.

A.8.2.1.3 Classification is determined by expert judgment, on the basis of the weight of all evidence available including the guidance presented below.

A.8.2.1.4 Weight of evidence of all available data, including human incidents, epidemiology, and studies conducted in experimental animals is used to substantiate specific target organ toxic effects that merit classification.

A.8.2.1.5 The information required to evaluate specific target organ toxicity comes either from single exposure in humans (e.g., exposure at home, in the workplace or environmentally), or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Results of acute toxicity studies conducted in other species may also provide relevant information.

A.8.2.1.6 In exceptional cases, based on expert judgment, it may be appropriate to place certain substances with human evidence of target organ toxicity in Category 2: (a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or (b) based on the nature and severity of effects. Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the chemical shall be classified as Category 1.

A.8.2.1.7 Effects considered to support classification for Category 1 and 2

A.8.2.1.7.1 Classification is supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect.

A.8.2.1.7.2 Evidence from human experience/incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

A.8.2.1.7.3 Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, and macroscopic and microscopic pathological examination and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and evidence relevance to human health, must be taken into consideration in the classification process. Relevant toxic effects in humans and/or animals include, but are not limited to:

(a) Morbidity resulting from single exposure;

(b) Significant functional changes, more than transient in nature, in the respiratory system, central or peripheral nervous systems, other organs or other organ systems, including signs of central nervous system depression and effects on special senses (e.g., sight, hearing and sense of smell);

(c) Any consistent and significant adverse change in clinical biochemistry, hematology, or urinalysis parameters;

(d) Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) Multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

(f) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction; and,

(g) Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

A.8.2.1.8 Effects considered not to support classification for Category 1 and 2

Effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) Clinical observations or small changes in bodyweight gain, food consumption or water intake that may have some toxicological importance but that do not, by themselves, indicate "significant" toxicity;

(b) Small changes in clinical biochemistry, hematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or of minimal toxicological importance;

(c) Changes in organ weights with no evidence of organ dysfunction;

(d) Adaptive responses that are not considered toxicologically relevant; and,

(e) Substance-induced species-specific mechanisms of toxicity, i.e., demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.

A.8.2.1.9 Guidance values to assist with classification based on the results obtained from studies conducted in experimental animals for Category 1 and 2

A.8.2.1.9.1 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (Category 1 vs. Category 2), dose/concentration "guidance values" are provided for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged.

A.8.2.1.9.2 Thus, in animal studies, when significant toxic effects are observed that indicate classification, consideration of the dose/concentration at which these effects were seen, in relation to the suggested guidance values, provides useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the dose/concentration).

A.8.2.1.9.3 The guidance value (C) ranges for single-dose exposure which has produced a significant non-lethal toxic effect are those applicable to acute toxicity testing, as indicated in Table A.8.1.

Table A.8.1: Guidance value ranges for single-dose exposures

		Guidance value ranges for:		
Route of exposure	**Units**	**Category 1**	**Category 2**	**Category 3**
Oral (rat)	mg/kg body weight	C ≤ 300	2000 ≥ C > 300	Guidance values do not apply
Dermal (rat or rabbit)	mg/kg body weight	C ≤ 1000	2000 ≥ C > 1000	
Inhalation (rat) gas	ppmV/4h	C ≤ 2500	20,000 ≥ C > 2500	
Inhalation (rat) vapor	mg/1/4h	C ≤ 10	20 ≥ C > 10	
Inhalation (rat) dust/mist/fume	mg/l/4h	C ≤ 1.0	5.0 ≥ C > 1.0	

A.8.2.1.9.4 The guidance values and ranges mentioned in Table A.8.1 are intended only for guidance purposes, i.e., to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values. Guidance values are not provided for Category 3 since this classification is primarily based on human data; animal data may be included in the weight of evidence evaluation.

A.8.2.1.9.5 Thus, it is feasible that a specific profile of toxicity occurs at a dose/concentration below the guidance value, e.g., < 2000 mg/kg body weight by the oral route, however the nature of the effect may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, e.g., ≥ 2000 mg/kg body weight by the oral route, and in addition there is supplementary information from other sources, e.g., other single dose studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification is the prudent action to take.

A.8.2.1.10 Other considerations

A.8.2.1.10.1 When a substance is characterized only by use of animal data the classification process includes reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

A.8.2.1.10.2 When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to single exposure to a substance,

the substance shall be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because specific target organ toxicity observed was considered not relevant or significant to humans, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.

A.8.2.1.10.3 A substance that has not been tested for specific target organ toxicity shall, where appropriate, be classified on the basis of data from a scientifically validated structure activity relationship and expert judgment-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

A.8.2.2 Substances of Category 3

A.8.2.2.1 Criteria for respiratory tract irritation

The criteria for classifying substances as Category 3 for respiratory tract irritation are:

(a) Respiratory irritant effects (characterized by localized redness, edema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. It is recognized that this evaluation is based primarily on human data;

(b) Subjective human observations supported by objective measurements of clear respiratory tract irritation (RTI) (e.g., electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids);

(c) The symptoms observed in humans shall also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of "irritation" should be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of classification for respiratory tract irritation;

(d) There are currently no scientifically validated animal tests that deal specifically with RTI; however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g., hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation; and,

(e) This special classification will occur only when more severe organ effects including the respiratory system are not observed as those effects would require a higher classification.

A.8.2.2.2 Criteria for narcotic effects

The criteria for classifying substances in Category 3 for narcotic effects are:

(a) Central nervous system depression including narcotic effects in humans such as drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, and vertigo are included. These effects can also be manifested as severe headache or nausea, and can lead to reduced judgment, dizziness, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness; and,

(b) Narcotic effects observed in animal studies may include lethargy, lack of coordination righting reflex, narcosis, and ataxia. If these effects are not transient in nature, then they shall be considered for classification as Category 1 or 2.

A.8.3 Classification criteria for mixtures

A.8.3.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for specific target organ toxicity following single exposure, repeated exposure, or both.

A.8.3.2 Classification of mixtures when data are available for the complete mixture

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture shall be classified by weight of evidence evaluation of this data. Care shall be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

A.8.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

A.8.3.3.1 Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data shall be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution, Batching, Concentration of mixtures, Interpolation within one toxicity category, Substantially similar mixtures, or Aerosols.

A.8.3.4 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A.8.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), following single exposure, repeated exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate cut-off value/concentration limit specified in Table A.8.2 for Categories 1 and 2, respectively.

Table A.8.2: Cut-off values/concentration limits of ingredients of a mixture classified as a specific target organ toxicant that would trigger classification of the mixture as Category 1 or 2

Ingredients classified as:	Cut-off values/concentration limits triggering classification of a mixture as:	
	Category 1	Category 2
Category 1 Target organ toxicant	≥ 1.0 %	
Category 2 Target organ toxicant		≥ 1.0 %

A.8.3.4.2 These cut-off values and consequent classifications shall be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

A.8.3.4.3 Mixtures shall be classified for either or both single and repeated dose toxicity independently.

A.8.3.4.4 Care shall be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

A.8.3.4.5 Care shall be exercised when extrapolating the toxicity of a mixture that contains Category 3 ingredient(s). A cut-off value/concentration limit of 20%, considered as an additive of all Category 3 ingredients for each hazard endpoint, is appropriate; however, this cut-off value/concentration limit may be higher or lower depending on the Category 3 ingredient(s) involved and the fact that some effects such as respiratory tract irritation may not occur below a certain concentration while other effects such as narcotic effects may occur below this 20% value. Expert judgment shall be exercised. Respiratory tract irritation and narcotic effects are to be evaluated separately in accordance with the criteria given in A.8.2.2. When conducting classifications for these hazards, the contribution of each ingredient should be considered additive, unless there is evidence that the effects are not additive.

A.9 SPECIFIC TARGET ORGAN TOXICITY REPEATED OR PROLONGED EXPOSURE

A.9.1 Definitions and general considerations

A.9.1.1 *Specific target organ toxicity - repeated exposure (STOT-RE)* means specific target organ toxicity arising from repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in A.1 to A.7 and A.10 of this Appendix are included. Specific target organ toxicity following a single-event exposure is classified in accordance with *SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE* (A.8 of this Appendix) and is therefore not included here.

A.9.1.2 Classification identifies the substance or mixture as being a specific target organ toxicant and, as such, it may present a potential for adverse health effects in people who are exposed to it.

A.9.1.3 These adverse health effects produced by repeated exposure include consistent and identifiable toxic effects in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or hematology of the organism and these changes are relevant for human health. Human data will be the primary source of evidence for this hazard class.

A.9.1.4 Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs.

A.9.1.5 Specific target organ toxicity can occur by any route that is relevant for humans, e.g., principally oral, dermal or inhalation.

A.9.2 Classification criteria for substances

A.9.2.1 Substances shall be classified as STOT - RE by expert judgment on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), (See A.9.2.9). Substances shall be placed in one of two categories, depending upon the nature and severity of the effect(s) observed, in accordance with Figure A.9.1.

Figure A.9.1: Hazard categories for specific target organ toxicity following repeated exposure

CATEGORY 1:	**Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated or prolonged exposure** Substances are classified in Category 1 for specific target organ toxicity (repeated exposure) on the basis of: (a) reliable and good quality evidence from human cases or epidemiological studies; or, (b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (See A.9.2.9) to be used as part of weight-of-evidence evaluation.
CATEGORY 2:	**Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated or prolonged exposure** Substances are classified in Category 2 for specific target organ toxicity (repeated exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (See A.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (See A.9.2.6).
Note: The primary target organ/system shall be identified where possible, or the substance shall be identified as a general toxicant. The data shall be carefully evaluated and, where possible, shall not include secondary effects (e.g., a hepatotoxicant can produce secondary effects in the nervous or gastro-intestinal systems).	

A.9.2.2 The relevant route of exposure by which the classified substance produces damage shall be identified.

A.9.2.3 Classification is determined by expert judgment, on the basis of the weight of all evidence available including the guidance presented below.

A.9.2.4 Weight of evidence of all data, including human incidents, epidemiology, and studies conducted in experimental animals, is used to substantiate specific target organ toxic effects that merit classification.

A.9.2.5 The information required to evaluate specific target organ toxicity comes either from repeated exposure in humans, e.g., exposure at home, in the workplace or environmentally, or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies (up to 2 years) that include hematological, clinico-chemical and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/organs to be identified. Data from repeat dose studies performed in other species may also be used. Other long-term exposure studies, e.g., for carcinogenicity, neurotoxicity or reproductive toxicity, may also provide evidence of specific target organ toxicity that could be used in the assessment of classification.

A.9.2.6 In exceptional cases, based on expert judgment, it may be appropriate to place certain substances with human evidence of specific target organ toxicity in Category 2: (a) when the weight of human evidence is not sufficiently convincing to warrant Category 1 classification, and/or (b) based on the nature and severity of effects. Dose/concentration levels in humans shall not be considered in the classification and any available evidence from animal studies shall be consistent with the Category 2 classification. In other words, if there are also animal data available on the substance that warrant Category 1 classification, the substance shall be classified as Category 1.

A.9.2.7 Effects considered to support classification

A.9.2.7.1 Classification is supported by reliable evidence associating repeated exposure to the substance with a consistent and identifiable toxic effect.

A.9.2.7.2 Evidence from human experience/incidents is usually restricted to reports of adverse health consequences, often with uncertainty about exposure conditions, and may not provide the scientific detail that can be obtained from well-conducted studies in experimental animals.

A.9.2.7.3 Evidence from appropriate studies in experimental animals can furnish much more detail, in the form of clinical observations, hematology, clinical chemistry, macroscopic and microscopic pathological examination and this can often reveal hazards that may not be life-threatening but could indicate functional impairment. Consequently all available evidence, and relevance to human health, must be taken into consideration in the classification process. Relevant toxic effects in humans and/or animals include, but are not limited to:

(a) Morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, or due to the overwhelming of the de-toxification process by repeated exposure;

(b) Significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g., sight, hearing and sense of smell);

(c) Any consistent and significant adverse change in clinical biochemistry, hematology, or urinalysis parameters;

(d) Significant organ damage that may be noted at necropsy and/or subsequently seen or confirmed at microscopic examination;

(e) Multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;

(f) Morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver); and,

(g) Evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

A.9.2.8 Effects considered not to support classification

Effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) Clinical observations or small changes in bodyweight gain, food consumption or water intake that may have some toxicological importance but that do not, by themselves, indicate "significant" toxicity;

(b) Small changes in clinical biochemistry, hematology or urinalysis parameters and /or transient effects, when such changes or effects are of doubtful or of minimal toxicological importance;

(c) Changes in organ weights with no evidence of organ dysfunction;

(d) Adaptive responses that are not considered toxicologically relevant;

(e) Substance-induced species-specific mechanisms of toxicity, i.e., demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.

A.9.2.9 Guidance values to assist with classification based on the results obtained from studies conducted in experimental animals

A.9.2.9.1 In studies conducted in experimental animals, reliance on observation of effects alone, without reference to the duration of experimental exposure and dose/concentration, omits a fundamental concept of toxicology, i.e., all substances are potentially toxic, and what determines the toxicity is a function of the dose/concentration and the duration of exposure. In most studies conducted in experimental animals the test guidelines use an upper limit dose value.

A.9.2.9.2 In order to help reach a decision about whether a substance shall be classified or not, and to what degree it shall be classified (Category 1 vs. Category 2), dose/concentration "guidance values" are provided in Table A.9.1 for consideration of the dose/concentration which has been shown to produce significant health effects. The principal argument for proposing such guidance values is that all chemicals are potentially toxic and there has to be a reasonable dose/concentration above which a degree of toxic effect is acknowledged. Also, repeated-dose studies conducted in experimental animals are designed to produce toxicity at the highest dose used in order to optimize the test objective and so most studies will reveal some toxic effect at least at this highest dose. What is therefore to be decided is not only what effects have been produced, but also at what dose/concentration they were produced and how relevant is that for humans.

A.9.2.9.3 Thus, in animal studies, when significant toxic effects are observed that indicate classification, consideration of the duration of experimental exposure and the dose/concentration at which these effects were seen, in relation to the suggested guidance values, provides useful information to help assess the need to classify (since the toxic effects are a consequence of the hazardous property(ies) and also the duration of exposure and the dose/concentration).

A.9.2.9.4 The decision to classify at all can be influenced by reference to the dose/concentration guidance values at or below which a significant toxic effect has been observed.

A.9.2.9.5 The guidance values refer to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. The assessment should be done on a case-by-case basis; for example, for a 28-day study the guidance values below would be increased by a factor of three.

A.9.2.9.6 Thus for Category 1 classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur at or below the (suggested) guidance values (C) as indicated in Table A.9.1 would justify classification:

Table A.9.1: Guidance values to assist in Category 1 classification (applicable to a 90-day study)

Route of exposure	Units	Guidance values (dose/concentration)
Oral (rat)	mg/kg body weight/day	C ≤ 10
Dermal (rat or rabbit)	mg/kg body weight/day	C ≤ 20
Inhalation (rat) gas	ppmV/6h/day	C ≤ 50
Inhalation (rat) vapor	mg/liter/6h/day	C ≤ 0.2

Inhalation (rat) dust/mist/fume	mg/liter/6h/day	C ≤ 0.02

A.9.2.9.7 For Category 2 classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur within the (suggested) guidance value ranges as indicated in Table A.9.2 would justify classification:

Table A.9.2: Guidance values to assist in Category 2 classification (applicable to a 90-day study)

Route of exposure	Units	Guidance values range (dose/concentration)
Oral (rat)	mg/kg body weight/day	10 < C ≤ 100
Dermal (rat or rabbit)	mg/kg body weight/day	20 < C ≤ 200
Inhalation (rat) gas	ppmV/6h/day	50 < C ≤ 250
Inhalation (rat) vapor	mg/liter/6h/day	0.2 < C ≤ 1.0
Inhalation (rat) dust/mist/fume	mg/liter/6h/day	0.02 < C ≤ 0.2

A.9.2.9.8 The guidance values and ranges mentioned in A.2.9.9.6 and A.2.9.9.7 are intended only for guidance purposes, i.e., to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values.

A.9.2.9.9 Thus, it is possible that a specific profile of toxicity occurs in repeat-dose animal studies at a dose/concentration below the guidance value, e.g., < 100 mg/kg body weight/day by the oral route, however the nature of the effect, e.g., nephrotoxicity seen only in male rats of a particular strain known to be susceptible to this effect, may result in the decision not to classify. Conversely, a specific profile of toxicity may be seen in animal studies occurring at above a guidance value, e.g., ≥ 100 mg/kg body weight/day by the oral route, and in addition there is supplementary information from other sources, e.g., other long-term administration studies, or human case experience, which supports a conclusion that, in view of the weight of evidence, classification is prudent.

A.9.2.10 Other considerations

A.9.2.10.1 When a substance is characterized only by use of animal data the classification process includes reference to dose/concentration guidance values as one of the elements that contribute to the weight of evidence approach.

A.9.2.10.2 When well-substantiated human data are available showing a specific target organ toxic effect that can be reliably attributed to repeated or prolonged exposure to a substance, the substance shall be classified. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a substance is unclassified because no specific target organ toxicity was seen at or below the dose/concentration guidance value for animal testing, if subsequent human incident data become available showing a specific target organ toxic effect, the substance shall be classified.

A.9.2.10.3 A substance that has not been tested for specific target organ toxicity may in certain instances, where appropriate, be classified on the basis of data from a scientifically validated structure activity relationship and expert judgment-based extrapolation from a structural analogue that has previously been classified together with substantial support from consideration of other important factors such as formation of common significant metabolites.

A.9.3 Classification criteria for mixtures

A.9.3.1 Mixtures are classified using the same criteria as for substances, or alternatively as described below. As with substances, mixtures may be classified for specific target organ toxicity following single exposure, repeated exposure, or both.

A.9.3.2 Classification of mixtures when data are available for the complete mixture

When reliable and good quality evidence from human experience or appropriate studies in experimental animals, as described in the criteria for substances, is available for the mixture, then the mixture shall be classified by weight of evidence evaluation of these data. Care shall be exercised in evaluating data on mixtures, that the dose, duration, observation or analysis, do not render the results inconclusive.

A.9.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

A.9.3.3.1 Where the mixture itself has not been tested to determine its specific target organ toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazards of the mixture, these data shall be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution; Batching; Concentration of mixtures; Interpolation within one toxicity category; Substantially similar mixtures; and Aerosols.

A.9.3.4 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A.9.3.4.1 Where there is no reliable evidence or test data for the specific mixture itself, and the bridging principles cannot be used to enable classification, then classification of the mixture is based on the classification of the ingredient substances. In this case, the mixture shall be classified as a specific target organ toxicant (specific organ specified), following single exposure, repeated exposure, or both when at least one ingredient has been classified as a Category 1 or Category 2 specific target organ toxicant and is present at or above the appropriate cut-off value/concentration limit specified in Table A.9.3 for Category 1 and 2 respectively.

Table A.9.3: Cut-off value/concentration limits of ingredients of a mixture classified as a specific target organ toxicant that would trigger classification of the mixture as Category 1 or 2

Ingredient classified as:	Cut-off values/concentration limits triggering classification of a mixture as:	
	Category 1	Category 2
Category 1 Target organ toxicant	≥ 1.0 %	
Category 2 Target organ toxicant		≥ 1.0 %

A.9.3.4.2 These cut-off values and consequent classifications shall be applied equally and appropriately to both single- and repeated-dose target organ toxicants.

A.9.3.4.3 Mixtures shall be classified for either or both single- and repeated-dose toxicity independently.

A.9.3.4.4 Care shall be exercised when toxicants affecting more than one organ system are combined that the potentiation or synergistic interactions are considered, because certain substances can cause specific target organ toxicity at < 1% concentration when other ingredients in the mixture are known to potentiate its toxic effect.

A.10 ASPIRATION HAZARD

A.10.1 Definitions and general and specific considerations

A.10.1.1 *Aspiration* means the entry of a liquid or solid chemical directly through the oral or nasal cavity, or indirectly from vomiting, into the trachea and lower respiratory system.

A.10.1.2 Aspiration toxicity includes severe acute effects such as chemical pneumonia, varying degrees of pulmonary injury or death following aspiration.

A.10.1.3 Aspiration is initiated at the moment of inspiration, in the time required to take one breath, as the causative material lodges at the crossroad of the upper respiratory and digestive tracts in the laryngopharyngeal region.

A.10.1.4 Aspiration of a substance or mixture can occur as it is vomited following ingestion. This may have consequences for labeling, particularly where, due to acute toxicity, a recommendation may be considered to induce vomiting after ingestion. However, if the substance/mixture also presents an aspiration toxicity hazard, the recommendation to induce vomiting may need to be modified.

A.10.1.5 Specific considerations

A.10.1.5.1 The classification criteria refer to kinematic viscosity. The following provides the conversion between dynamic and kinematic viscosity:

$$\frac{\text{Dynamic viscosity (mPa·s)}}{\text{Density (g/cm}^3\text{)}} = \text{Kinematic viscosity (mm}^2\text{/s)}$$

A.10.1.5.2 Although the definition of aspiration in A.10.1.1 includes the entry of solids into the respiratory system, classification according to (b) in table A.10.1 for Category 1 is intended to apply to liquid substances and mixtures only.

A.10.1.5.3 Classification of aerosol/mist products

Aerosol and mist products are usually dispensed in containers such as self-pressurized containers, trigger and pump sprayers. Classification for these products shall be considered if their use may form a pool of product in the mouth, which then may be aspirated. If the mist or aerosol from a pressurized container is fine, a pool may not be formed. On the other hand, if a pressurized container dispenses product in a stream, a pool may be formed that may then be aspirated. Usually, the mist produced by trigger and pump sprayers is coarse and therefore, a pool may be formed that then may be aspirated. When the pump mechanism may be removed and contents are available to be swallowed then the classification of the products should be considered.

A.10.2 Classification criteria for substances

Table A.10.1: Criteria for aspiration toxicity

Category	Criteria
Category 1: Chemicals known to cause human aspiration toxicity hazards or to be regarded as if they cause human aspiration toxicity hazard	A substance shall be classified in Category 1: (a) If reliable and good quality human evidence indicates that it causes aspiration toxicity (See note); or (b) If it is a hydrocarbon and has a kinematic viscosity ≤ 20.5 mm^2/s, measured at 40° C.

Note: Examples of substances included in Category 1 are certain hydrocarbons, turpentine and pine oil.

A.10.3 Classification criteria for mixtures

A.10.3.1 Classification when data are available for the complete mixture

A mixture shall be classified in Category 1 based on reliable and good quality human evidence.

A.10.3.2 Classification of mixtures when data are not available for the complete mixture: bridging principles

A.10.3.2.1 Where the mixture itself has not been tested to determine its aspiration toxicity, but there are sufficient data on both the individual ingredients and similar tested mixtures to adequately characterize the hazard of the mixture, these data shall be used in accordance with the following bridging principles as found in paragraph A.0.5 of this Appendix: Dilution; Batching; Concentration of mixtures; Interpolation within one toxicity category; and Substantially similar mixtures. For application of the dilution bridging principle, the concentration of aspiration toxicants shall not be less than 10%.

A.10.3.3 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

A.10.3.3.1 A mixture which contains ≥ 10% of an ingredient or ingredients classified in Category 1, and has a kinematic viscosity ≤ 20.5 mm^2/s, measured at 40 °C, shall be classified in Category 1.

A.10.3.3.2 In the case of a mixture which separates into two or more distinct layers, one of which contains ≥ 10 % of an ingredient or ingredients classified in Category 1 and has a kinematic viscosity ≤ 20.5 mm^2/s, measured at 40 °C, then the entire mixture shall be classified in Category 1.

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Next Standard (1910.1200 App B)

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