

# Development of Permissible Exposure Limits:

## The California Experience

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The California OSHA Airborne Contaminant Advisory Committee reviewed several hundred substances and recommended occupational exposure limits with the intent of worker and employer protection. The model used offers important benefits. First, by allowing open meetings, the process was transparent, and input could be offered by concerned stakeholders. Second, the process was data-driven and, therefore, less susceptible to bias and error. Third, by incorporating members with backgrounds in toxicology, epidemiology, risk assessment, occupational medicine, and industrial hygiene, the process fostered a thorough and diverse assessment of substances. *Key words:* occupational exposure limits; standards; regulation; California.

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In 1973 California implemented Cal/OSHA (California Occupational Safety and Health Administration), a state OSHA plan. For selected hazards or substances Cal/OSHA convenes advisory committees consisting of technical experts selected from industry, labor, academia, and other interested parties. The committee is provided a charter or assignment by the Cal/OSHA administrative staff, and meetings are facilitated and recorded by Cal/OSHA. The purpose of the committee is to determine whether or not the regulation of a specific potential occupational hazard is indicated and, if so, to recommend the structure and content of such a regulation.

The Airborne Contaminant Advisory Committee has been convened periodically since 1977 for the purpose of recommending occupational airborne exposure limits for hazardous substances. Typically, each committee has been asked by the Cal/OSHA staff to evaluate approxi-

mately 50 agents, for each of which the American Conference of Governmental Industrial Hygienists (ACGIH) has recently recommended a change in a threshold limit value (TLV) that caused the TLV to differ from the California permissible exposure limit (PEL).

Advisory committee membership has been voluntary. Members are selected by Cal/OSHA from stakeholders and academia based on the members' expertise. The six current members (the authors) have extensive experience and recognized expertise in industrial hygiene, epidemiology, occupational medicine, environmental health, and/or industrial toxicology. Most, if not all, of the data analysis and literature review necessary has been performed by the individual members. The process of reviewing approximately 50 substances has usually required two to three years. Upon completion of this process, documentation of the findings and justification of committee recommendations has been prepared by Cal/OSHA staff. Cal/OSHA staff subsequently presented to the California Occupational Safety and Health Standards Board its proposed changes based on the committee's recommendations; the Standards Board then has had public discussion and opportunities for presentations and comments by interested parties. The Standards Board has then decided whether or not to adopt the proposals as regulations.

The purpose of this article is to describe the process by which the most recent Airborne Contaminants Advisory Committee developed its recommendations. An awareness and understanding of this process may be of use to private and public entities with similar responsibilities and to those affected by the outcomes of this rule-making process.

### PROCESS

To accomplish an exposure-response assessment, each substance was assigned to an individual committee member such that one member researched a given substance. He or she then presented the findings and PEL recommendation to the entire committee for review.

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The individual assessments have usually included a review of the most recent ACGIH TLV documentation, other published risk assessments (e.g., Environmental Protection Agency (EPA), Office of Environmental Health Hazard Assessment (OEHHA)), and a literature search for data regarding hazard identification, exposure–response relationships, and toxicologic mechanism for that substance. Both animal and human data were considered although greater reliance was usually placed on human data. Common sources of data have included PubMed, TOXNET, and government agencies, including OSHA, EPA, California OEHHA, and the National Toxicology Program (NTP). Information has also been acquired from industry, labor, and environmental organizations, although greater reliance has usually been placed on published, peer-reviewed sources.

At each meeting a few substances were discussed in detail. The member who had reviewed collected, and analyzed the dose-effect data presented their analyses to the remainder of the committee. Appendix A is an example of a worksheet (“Glyoxal”) that exemplifies the information developed and presented by any one committee member for the full committee’s deliberations. Individual studies relied upon by the presenting member were discussed and often challenged by other members. Many times, additional data or supporting documentation was requested by other members prior to a final decision. After all members were satisfied with the quantity and quality of the data assessment, a proposal for a PEL was offered and voted upon. Where significantly differing opinions remained, further discussion ensued and additional proposals were offered until a consensus was reached. On rare occasions there were one or two dissenters from the majority position. The committee also specified that the proposed limit involved skin exposure, a short-term exposure limit, an eight-hour time-weighted average or a ceiling value.

## GENERAL CONSIDERATIONS

For non-carcinogens, the goal has been to determine the highest “no observable adverse effect level” (NOAEL). In recent years it has been the committee’s philosophy that the exposure limit should represent the highest human NOAEL. Committee members’ personal experiences had led them to believe that this was consistent with the expectations of workers and practicing health, safety and industrial hygiene professionals. Also, the PEL represented the highest “no-observable effect” level for the most sensitive health impact attributed to the specific agent. Appendix B provides an overview of the data-evaluation process for non-cancer outcomes. This process was based on that used by pharmaceutical industry industrial hygienists to develop occupational exposure limits for active pharmaceutical agents.<sup>1</sup>

In the late 1990s there was recognition that cancer-risk assessment had not been incorporated into the commit-

tee’s deliberations and recommendations. For this reason the most recent committee began relying on published and authoritative cancer risk assessments to ensure that the recommended exposure limits included cancer exposure–response considerations (Appendix C).

For both carcinogens and non-carcinogens the most recent committee relied most heavily on those studies providing quantifiable exposure–response data. Consideration was also given to the severity of the health outcome and to the type of exposure-measurement technique and its reliability. Studies were scrutinized for their techniques, and greater weight tended to be given to those studies that appeared more credible based on peer review, study design, and other epidemiologic criteria. In some cases only one study with the most sensitive outcome was relied upon for the exposure limit, while in others a midrange of data may have been selected for an exposure limit for those health effects with less health impact, such as acute irritation. Such choices were usually based on type and severity of health outcome.

The committee recognized that studies reporting subjective effects may not be indicative of physiologic effects or pathology. It also recognized that in some cases subjective effects may have been precursors or early indicators of exposures that if continued over a long term could result in physiologic effects such as sensitization or neurasthenia. Whenever possible the committee relied more heavily on human data. Where human data were inadequate, animal data received greater scrutiny and reliance.

For most substances clear and specific NOAELs were unknown. In such cases the committee often chose to apply “uncertainty” or “safety” factors to higher exposure–effect levels in an attempt to estimate a “no-effect” level.<sup>2</sup> Over the years there were repeated and continual discussions regarding the circumstances and sizes of uncertainty factors. It was usual practice to apply an uncertainty factor to animal studies when using animal data as an estimate of human exposure–response relationships. Additionally, it was agreed that for health outcomes of greater severity, such as cancer or reproductive toxicity, larger uncertainty factors were appropriate. The sizes and specific applications of uncertainty factors were not uniform. Instead, a factor was determined specifically for each substance based on the unique toxicology associated with that substance. For example, sensitizers were more likely to have higher uncertainty factors than simple irritants. There were differences in uncertainty factors due also to variations in the data and the sources of the data (animal versus human), as well as consistency between studies. Appendix B provides examples of the magnitudes and circumstances of the uncertainty factors applied by the committee.

The committee’s recommendations were based on the toxicology and the health impact of a given substance.<sup>3</sup> Thus, the Committee’s assignment was to rec-

commend safety-based exposure limits; cost-benefit considerations regarding the exposure limits were not assessed. There was some discussion regarding detection technologies and capabilities, but most often those considerations were largely deleted from the determination of the “no-effect” level and subsequent recommendation. Frequently circumstances were such that additional publications were requested by the committee for review and decisions were postponed to subsequent meetings to enable such review, in order for members to achieve a majority position or consensus.

Committee meetings were public, and at many meetings various stakeholders (usually representing companies, industrial sectors, or employee organizations) presented data intended to assist the committee in its evaluation of scientific literature. The committee sought specific exposure-response data from the presenters and scrutinized such data when they were provided. Technical representatives of industry and government agencies were helpful in discussions of scientific data. In some cases the original investigators were present to discuss their research.

Most of the substances evaluated by the committee had relatively sparse human exposure-response data and, in some cases, few analogous animal data. The committee recognized that its process included arguable assumptions and the application of uncertainty factors that could be either inadequate or excessive. It also understood that data to resolve these uncertainties were unlikely to be forthcoming in the near future. The committee recognized that there were some substances for which the data were so inadequate that recommendations for exposure limits were not possible. Although the committee members were from a variety of constituencies and backgrounds, it was remarkable that there was little controversy regarding the exposure limits ultimately recommended for each substance.

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## APPENDIX A

### *Example of a Substance-specific Data/Worksheet Presented to the Committee*

#### **GYLOXAL**

Data sources: PubMed, Toxnet (IRIS, HSDS...); BG Chemie Toxicological Evaluation 12 1998; ACGIH document

Uses: multiple: textiles, glue, pesticides, disinfectant...

Form: yellow crystals, melting point = 15C, boiling point = 52C.

ACGIH: New TLV = 0.1 mg/m<sup>3</sup>

#### **Selected subchronic oral studies**

Route	Length	Animal	Doses	Effect	NOEL/LOEL	Reference
Drinking water	28 day	Rats	300 and 1000 mg/kg	Decreased body weight gain	NOEL = 100 mg/kg	CIT, 1987
Feeding	3 month	Rats			NOEL = 125 mg/kg	Mellon, 1966

Drinking water	3 month	Rats	2000, 4000, 6000 mg/L	Decreased food intake, BW gain, decreased serum protein levels at all doses.	LOEL = 107 mg/kg	Ueno, 1991
Drinking water	3 month	Rats/ mice	1000, 2000 ... 16,000 mg/L	Minor lymphoid hyperplasia, hemorrhage of mesenteric lymph nodes at all doses (rats)	mg/kg not given	NTP, 1991
Feeding	3 month	Dogs	31, 65, 115 mg/kg	No effects at any dose	NOEL = 115 mg/kg	Mellon 1966

#### Other studies:

Type	Findings	Reference
Teratogen studies	No effect at 1000 mg/kg, the highest dose studied	BG Chemie
Repro. studies	No studies found	
Genotoxicity/ Mutagenicity:	Many positive studies	BG Chemie
Sensitization	Several positive studies in animals and humans.	Takahashi, 1989
Animal cancer	Acts as a promoter in stomach cancer in rats, 0.5% glyoxal in water. Increased rate of stomach cancer was 2-fold when given with an initiator. No tumors when glyoxol was given alone.	
Animal cancer	Not a promoter in skin cancer study	Miyakawa, 1991
Human cancer	No studies found	
<b>Animal inhalation (only one study found)</b>	<ul style="list-style-type: none"> <li>• 10 rats at each dose group</li> <li>• Doses: 0, 0.4, 2.0, 10 mg/m<sup>3</sup> (40% solution as an aerosol)</li> <li>• 6 hrs/day, 5 days/week over 29 days</li> </ul> <p>Author: Hoechst AG: unpublished. Results are from the review of this study in BG Chemie Toxicological Evaluation Vol. 12. 1998. (Ref # 23 in ACGIH document)</p>	<p>No visible signs of toxicity No effects on body weight gain, food intake, urinalysis, hematological or chemical findings. Two highest doses showed a "minimum squamous metaplasia of the epiglottal epithelium in the larynx that was accompanied by a minimum submucous lymphoid cell infiltration". This was not seen in the 0.4 mg/m<sup>3</sup> group NOEL = 0.4 mg/m<sup>3</sup></p>

#### Related chemicals:

Chemical	LC50	RD50	Notes
Formaldehyde	81 ppm	5.3-13 ppm	Dose-response nasal cancer and squamous metaplasia in 2-yr rat study at 2, 6, and 14 ppm. IARC: probable human carcinogen.
Acetaldehyde	13,300 ppm	2845 ppm	Animal carcinogen
Acrolein	16 ppm (LC100)	0.88-0.97 ppm	
Crotonaldehyde	600-1500 ppm	3.5-4.9 ppm	
Glutaraldehyde	5000 ppm	14 ppm	Contact dermatitis
Glyoxal	2440 ppm (40%)	Unknown?	

#### Risk Assessment Notes:

Only one animal inhalation study. NOEL = 0.4 mg/m<sup>3</sup>

No studies in humans.

There is some evidence that glyoxal may have carcinogenic properties:

- Many positive genotoxicity studies
- Some evidence that glyoxal may act as a tumor promoter (stomach cancer in rats).
- Structural similarity to other possible carcinogens

Therefore, although there is not enough data or evidence to justify a formal cancer risk assessment, the cancer potential may argue for a more conservative strategy when assigning safety factors in the non-cancer risk assessment.

Safety Factor	NOEL = 0.4 mg/m <sup>3</sup>	NOEL = 0.4 mg/m <sup>3</sup>	NOEL = 0.4 mg/m <sup>3</sup>
Animal to human	10	3	3
Subchronic to chronic	10	3	3
6 hours/day to 8 hours/day	1.33	1.33	1.33
Human variability	10	3	0
LOEL to NOEL	0	0	0
Severe outcome	0	0	0
<b>Total safety factors/adjustments</b>	<b>1330</b>	<b>40</b>	<b>12</b>
<b>TLV</b>	<b>0.0003 mg/m<sup>3</sup></b>	<b>0.01 mg/m<sup>3</sup></b>	<b>0.03 mg/m<sup>3</sup></b>
	<i>Most conservative</i>		<i>Least conservative</i>

### Questions:

Which safety factors are appropriate?

Convert oral doses? Are the NOELs consistent with the NOEL from the inhalation study?

RDGR to convert exposures in animals to human dose equivalents?

## APPENDIX B

### *Permissible-exposure-limit Development Process*

1. Search databases for documents that may include animal or human exposure-response data (e.g., PubMed, TOXNET, EPA, NTP, NIOSH).
2. Retrieve and review documents to identify the following information: daily dose (usually an 8 hour TWA), health outcome (symptoms, pathology, laboratory abnormality), duration of dosing, number of subjects, human or animal, route of administration, and citation.
3. Identify relevant toxicokinetic data including biological half-life and bioavailability following inhalationairborne and/or skin exposure.
4. For each exposure-response data point identify a safety/uncertainty factor for species differential, if applicable. Factors from 3–10 are often used for animal studies.
5. If exposure is expressed as per kilogram or surface area, use 70 or 1.5 respectively to correct for a human adult weight or body surface.
6. Identify a safety/uncertainty factor for each exposure-response data point (reported exposure level) depending upon the severity or type of outcome. For example, “no observable adverse effect levels” could have a safety factor of 1.0. Studies having mild and reversible health effects could have a safety factor of 10; studies having health outcomes which could increase risk of death could have a safety factor of 100; studies having an outcome of cancer, reproductive toxicity or death could have a safety factor of 1,000; studies having mild, reversible health outcomes but that are also associated with allergy/hypersensitivity could have a safety factor of 100.
7. Application of safety factors should vary with the strength and character of the data.
8. Determine the average adult workday ventilation volume. This number would usually be 10 m<sup>3</sup>.
9. Using the relevant factors and exposure-response data taken from each study calculate an extrapolated exposure level according to the following formula:

$$\frac{\text{Daily dose from study} \times \text{body weight or surface area correction}}{\text{Susceptibility factor} \times \text{Species factor} \times \text{Severity factor} \times \text{Daily air volume}}$$

9. Create a table showing each calculated or reported air level, unique study characteristics and related data (below).

Species Studied.	Outcome.	# Subjects.	Study aspects.	Reported air level.	Citation.
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10. Based on the data distribution, assumptions used, health outcomes observed, toxicokinetics and other factors, the committee recommends an exposure limit and provides the justification.

## APPENDIX C

### *Permissible Exposure Limit Development Process for Carcinogens*

The basic principles outlined in the July 1999 Guidelines for Carcinogen Risk Assessment Review Draft Chemicals are used to establish potency estimates for lifetime workplace exposures (EPA 1999). Cancer risk assessments published by the EPA, Integrated Risk Information System are used when available with appropriate conversion from environmental to occupational exposures when necessary. Other cancer risk assessments published in peer-reviewed journals are also considered. When these are not available, the following methods are employed:

#### 1. Hazard Identification:

Databases such as TOXNET and PubMed are searched for all relevant human epidemiological and laboratory animal studies. Other data on mutagenicity, toxicokinetics, bio-markers, precursor effects of other mode of action information is also considered. A weight of the evidence approach for potential carcinogenicity to humans similar to that described in the EPA draft document is employed.

#### 2. Dose-Response Assessment;

- a) **Selecting data:** Appropriate dose-response data is selected based on quality and execution of the study, the target organs assessed, route of exposure, the length of the study relative to lifetime exposures, the adequacy of the dosing regimens, the magnitude of the responses, species sensitivity, species sensitivity and other possible mechanistic criteria. Data from human studies is preferred over animal data. When animal studies are used, human equivalent exposures are calculated and used in the following dose-response assessments. Pharmacokinetic data, if available, may be used to extrapolate from animal to human exposures.
- b) **Curve-fitting:** Typically, dose-response information from studies involving high exposures must be extrapolated to estimate risks at lower doses. To do this, curve fitting models are used to assess the dose-response relationship in the range of observable effects. Once the model is fitted to the available data, a line is then drawn from a point of departure in the observable range to the origin where no extra risk is expected. The LED<sub>10</sub> (the lower 95% confidence interval on the dose estimated to cause a ten percent response) is usually selected as the point of departure since a ten percent response is the lowest level of detection in most cancer studies.
- c) **Extrapolation:** By linearly extrapolating from the point of departure, the average daily lifetime workplace exposures associated with added cancer risks from 1 in 1000 to 1 in 10,000 are then estimated. For compounds where there is strong evidence that a non-linear dose-response relationship is present, a NOEAL/LOEAL is selected and a margin of exposure approach is considered.