Occupational Health Hazard Risk Assessment Project for California

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Introduction

- Project conceived by Dr. Julia Quint of HESIS
- Build on previous efforts by HESIS to apply risk assessment methods to:
  - Identify chemicals of concern to workers
  - Develop protective occupational exposure limits
- Engage OEHHA to conduct systematic analysis
Background on OEHHA

- The “scientific arm” of Cal/EPA
- Lead agency for risk assessment in California
- Risk assessments conducted under various mandates:
  - Proposition 65: Carcinogens and reproductive/developmental toxicants
  - Water Program: Public Health Goals
  - Air Program: Toxic Air Contaminants, Hot Spots, Criteria Air Pollutants
Primary Goals of Project

- Screen Proposition 65 list for workplace chemicals of concern
  - Evidence of current use in a workplace; and
  - Unregulated or under-regulated in the occupational setting

- Describe and apply methods for calculating health protective air concentrations

- Discuss scientific issues related to dose-response assessment for the occupational setting

- Provide input to HESIS on priorities for further evaluation
PROPOSITION 65 LIST

- State is required to maintain a list of chemicals identified as causing cancer and/or reproductive/developmental toxicity

- Chemicals have been added to the list under the following mechanisms:
  - Reference to Labor Code
  - Court order
  - State’s qualified experts
  - Formally required by a state or federal agency to be identified or labeled
  - Formally identified by an authoritative body
    - IARC
    - NIOSH
    - NTP (CERHR for reproductive toxicants)
    - US EPA
    - US FDA
Sufficient Evidence of Cancer

- Studies in humans indicate that there is a causal relationship between exposure to the chemical and induction of cancer; or
- Studies in animals show an increased incidence of tumors
  - in multiple species or strains;
  - in multiple experiments; or
  - in a single experiment to an unusual degree with regard to high incidence, site or type of tumor, or age at onset.
Criteria for Reproductive Toxicity

- Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity; or
- Sufficient data exist in experimental animals to indicate that an association between adverse reproductive effects in humans and the toxic agent is biologically plausible, taking into account factors including:
  - adequacy of the experimental design;
  - route of administration;
  - frequency and duration of exposure;
  - numbers of test animals;
  - choice of species;
  - choice of dosage levels; and
  - consideration of maternal toxicity.
Screening for “Workplace Chemicals” on Proposition 65 List

- **Determine identity/uses of chemical**
  - Sources such as HSDB, NTP Report on Carcinogens

- **Remove certain types**
  - Regulated largely by other agencies (e.g., pesticides, drugs)
  - Consumer products (e.g., alcohol, tobacco)
  - Certain byproducts (e.g., dioxin)
  - Certain mixtures (e.g., carbon black extracts)
  - Other (e.g., banned chemicals, research chemicals)
Screening for “Workplace Chemicals” on Proposition 65 List (cont.)

- Determine evidence of current use
  - TSCA 2002 Inventory Update Rule data
  - Other sources (e.g., USGS)
- Retain chemicals:
  - Likely to be present in a workplace; and
  - With evidence of current use

Inventory of chemicals used in California workplaces not available
Cal/OSHA PELs

- PEL availability and values determined by consulting:
  - http://www.dir.ca.gov/Title8/5155table_ac1.html

- PEL basis, if available, determined by consulting:
  - Vertical standard
  - Statement of reasons
Unregulated “Workplace” Chemicals

Workplace chemicals on Proposition 65 List that do not have PELs (as of Dec., 2006):

- 44 chemicals listed as known to cause cancer
- 5 chemicals listed as known to cause reproductive/developmental toxicity
Under-Regulated Carcinogens

- 62 workplace chemicals listed as known to cause cancer are not specifically regulated as occupational carcinogens

- In setting the PELs for some of these, cancer as a health endpoint was considered but risk assessments were not conducted
14 workplace chemicals listed as known to cause reproductive/developmental toxicity have PELs that either
- Do not explicitly account for this health endpoint;
  or
- Have an unclear basis

Some of these are regulated as occupational carcinogens and may have sufficiently protective PELs
Cancer and Noncancer Risk Assessment

- Identify available cancer unit risk values and noncancer health assessment values for workplace chemicals of concern
- Apply cancer risk assessment methods, with adjustments for workers, to:
  - Evaluate current PELs relative to 1 in 1,000 cancer risk
  - Calculate air concentrations associated with specified risk levels
- Apply noncancer risk assessment methods, with adjustments for workers, to:
  - Develop health protective air concentrations for selected chemicals
Information for Priority Setting

- Table 19 – Workplace chemicals known to cause cancer but not regulated as an occupational carcinogen
  - Is PEL available?
  - Basis for PEL, if known
  - Possible basis for PEL (comparison to other values such as TLV)
  - Availability of unit risk value
  - Estimated cancer cases per 1,000 workers exposed at the PEL
Information for Priority Setting (cont.)

- Table 20 – Workplace chemicals known to cause reproductive/developmental toxicity and not explicitly regulated for that endpoint
  - Is PEL available?
  - Basis for PEL, if known
  - Possible basis for PEL
  - Availability of noncancer health assessment values
The Four Steps of Risk Assessment

- **Hazard identification**
  - Determine the types of health effects a chemical could cause - cancer or noncancer

- **Toxicity or dose-response assessment**
  - Determine the relationship between levels of exposure to a chemical and the probability of health effects

- **Exposure assessment**
  - Estimate how much of a chemical a person is exposed to under particular circumstances

- **Risk characterization**
  - Combine the dose-response and exposure assessments to
    - Estimate the level of risk
    - Determine acceptable level of exposure
Risk Management

- Risk assessors provide scientific input to risk managers
  - Health protective levels of exposure
  - Options for reducing risk
- Risk managers separately consider other factors
  - Economic considerations
  - Technical feasibility
  - Stakeholder concerns
Cancer Risk Assessment Basics

- Some risk is assumed at any dose of a carcinogen.
- The “cancer potency” is expressed as the excess risk of cancer per unit exposure – i.e., a measure of the probability of developing cancer at a given exposure to a carcinogen.
- Cancer potencies are calculated by assuming lifetime exposure to a chemical for an adult male.
- Sensitive subpopulations and early lifestages are not typically considered.
Cancer Risk Assessment Methods

- Cancer risk assessments are typically developed for an adult male that is exposed for life (70 years).

- The shorter duration of worker exposure must be accounted for based on an assumed scenario:
  - 8 hours per day
  - Breathing rate of 10 m$^3$ per 8 hour work day (out of 20 m$^3$ per 24 hours)
  - 5 days per week
  - 50 weeks per year
  - 40 working years per a 70 year lifetime
Cancer Example 1: Hexachlorobenzene

- Listed under Proposition 65 as known to cause cancer (1987) and developmental toxicity (1989)

- Cal/OSHA PEL: 0.002 mg/m\(^3\) (or 2 µg/m\(^3\))
  - Based on hepatic and neurological effects; hepatic tumors in animals noted
  - Cal/OSHA Advisory Committee acknowledged HCB to be a carcinogen
    - PEL based on other effects due to lack of policy and resources to conduct risk assessment

- OEHHA unit risk value: 0.00051 (µg/m\(^3\))\(^{-1}\)
Understanding the Unit Risk Value

Definition:
The excess cancer risk associated with a continuous lifetime inhalation exposure to a unit air concentration (e.g., 1 μg/m³) of a given chemical.

The hexachlorobenzene unit risk value can be understood most simply as follows:
If 10,000 people inhaled 1 μg/m³ of HCB every day for life, approximately 5 excess cases of cancer would be expected in that population.
Cancer Risk Associated with Current Cal/OSHA PEL for Hexachlorobenzene

- **Cancer risk at current Cal/OSHA PEL:**

  \[
  \text{Risk} = \frac{0.00051 \text{ (μg/m}^3\text{)}^{-1}}{1} \times 2 \text{ μg/m}^3 \times \frac{10}{20} \times \frac{5}{7} \times \frac{50}{52} \times \frac{40}{70} = 2 \times 10^{-4}
  \]

  Unit Risk  \hspace{2cm} PEL \hspace{2cm} Worker Exposure Factors

- Also can be expressed as “2 in 10,000”

- Compared to “acceptable” cancer risk levels (determined by risk managers):
  - 1 in 100,000 under Proposition 65
  - 1 in 1,000 commonly applied for workplace
Cancer Example 2: Benzyl Chloride

- Listed under Proposition 65 as known to cause cancer (1990)

- Cal/OSHA Permissible Exposure Limit (PEL): 1 ppm (or 5 mg/m$^3$)
  - Same as ACGIH TLV
  - Likely based on eye, skin, URT irritation

- OEHHA unit risk value: 0.049 (mg/m$^3$)$^{-1}$
Cancer Risk Example Calculations for Benzyl Chloride

- **Cancer risk at current Cal/OSHA PEL:**

  \[
  \text{Risk} = 0.049 \times 5 \times \frac{10}{20} \times \frac{5}{7} \times \frac{50}{52} \times \frac{40}{70} = 5 \times 10^{-2}
  \]

- **Health-based exposure level \( C_{\text{occ}} \) associated with cancer risk of 1 in 1,000:**

  \[
  C_{\text{occ}} = \frac{0.001 \times 20 \times 7 \times 52 \times 70}{0.049 \times 10 \times 5 \times 50 \times 40} = 0.1 \text{ mg/m}^3
  \]
Interpreting High Cancer Risk Estimates

- **Exposure considerations**
  - Screening level risk assessment assumes worker exposed at the PEL for entire working life
  - Real world exposures may be far less

- **Dose-response considerations**
  - For most of the workplace chemicals assessed in the report, epidemiological studies are not available
  - In cases with high estimated risks, human dose at PEL comparable to animal dose that produced tumors in experimental studies
## Comparison of Worker and Animal Doses

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Worker Dose Based on PEL(^1) (mg/kg-day)</th>
<th>Lowest Animal Dose(^2) Producing Tumors (mg/kg-day)</th>
<th>Ratio Animal Dose: Worker Dose (no scaling)</th>
<th>Human Equivalent Dose (surface area scaling)</th>
<th>Ratio of Human Equivalent Dose: Worker Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis(2-chloroethyl) ether</td>
<td>2</td>
<td>40 ⇒ 88% tumor</td>
<td>20</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>Methylaziridine</td>
<td>0.3</td>
<td>3 ⇒ 81% tumor</td>
<td>10</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>3</td>
<td>6 ⇒ 14% tumor</td>
<td>2</td>
<td>1</td>
<td>0.33 (workers have higher dose)</td>
</tr>
<tr>
<td>Phenylhydrazine</td>
<td>1</td>
<td>13 ⇒ 53% tumor</td>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1. Assumes worker breathes 10 m\(^3\) during the workday, and works 5 d/wk, 50 wk/yr, 40 yr out of a 70 yr lifespan.
2. Lowest non-zero dose in bioassay(s) underlying cancer potency. Control rates: 10%, 0%, 0%, 13%, respectively.
Finding Occupational Cancer Cases

- **Cancer is inherently difficult to study**
  - Long latency period - disease may first appear 10 to 30 years after exposure
  - Occupational exposures difficult to characterize

- **Insufficient study for most known carcinogens**
  - Systematic follow up of exposed workers often not done
  - Insufficient occupational data collected by cancer registries
  - Few epidemiological studies conducted
Noncancer Risk Assessment Basics

- Assume that there is a threshold exposure level below which no significant adverse health effect would be expected.
- Typically conducted for the general population continuously exposed for life, with consideration of sensitive subpopulations.
- Identify or estimate a “no observed adverse effect level” (NOAEL) based on studies in animals or humans.
  - Benchmark dose/concentration can be used here.
Apply a series of uncertainty factors to estimate an exposure level considered “safe” for a population under specified exposure conditions

- Lowest observed adverse effect level (LOAEL) to NOAEL
- Subchronic to chronic
- Interspecies
- Intraspecies ← possibly adjust for occupational setting

Adjust assessment to account for shorter duration of worker exposure
Examples of Noncancer Health Assessment Levels

- **Chronic Reference Exposure Level (cREL):**
  - The concentration at or below which no adverse health effects are anticipated in the general population assuming continuous inhalation exposure

- **Maximum Allowable Dose Level (MADL):**
  - Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect

- **Reference Concentration (RfC):**
  - The concentration that is likely to be without an appreciable risk of deleterious effects to the human population (including sensitive subgroups) assuming continuous inhalation exposure
Noncancer Example: Benzene

- Noncancer effects: developmental and male reproductive toxicity; hematopoietic and nervous system toxicity
- Cal/OSHA PEL: 1 ppm
  - Regulated as an occupational carcinogen; PEL does not explicitly account for developmental/reproductive toxicity
- ACGIH TLV: 0.5 ppm
  - Leukemia
- OEHHA inhalation MADL: 49 µg/d
  - Altered blood cell formation in neonates
- OEHHA cREL: 0.02 ppm
  - Lowered red and white blood cell counts
  - Worker study
- U.S. EPA RfC: 0.01 ppm
  - Decreased lymphocyte count
  - Worker study
Example Health-Based Occupational Assessment based on Benzene cREL

- Study population: 303 refinery workers (Tsai et al., 1983)
- Critical effect: Hematological effects
- NOAEL: 0.53 ppm ← start with worker NOAEL
- LOAEL factor: 1
- Subchronic factor: 1
- Interspecies factor: 1
- Intraspecies factor: 1, 3 or 10 ← possible worker values
- Cumulative uncertainty factor: 1, 3 or 10
- Example health-based occupational air concentrations: 0.05, 0.2, or 0.5 ppm

- For this worker study, no adjustment for exposure needed
Example Health-Based Occupational Assessment based on Benzene RfC - U.S. EPA Approach

- Study population: 44 factory workers (Rothman et al., 1996)
- Critical effect: Hematological effects
- BMCL: 7.2 ppm ← start with worker BMCL, EPA method
- Effect level factor: 3
- Subchronic factor: 3
- Interspecies factor: 1
- Intraspecies factor: 1, 3 or 10 ← possible worker values
- Database deficiency factor: 3
- Cumulative uncertainty factor: 30, 100 or 300
- Example health-based occupational air concentrations: 0.02, 0.07, 0.2 ppm

- For this worker study, no adjustment for exposure needed
Example Health-Based Occupational Assessment based on Benzene MADL

- Study population: Mice exposed *in utero*
- Critical effect: Altered blood cell formation
- LOAEL: 5 ppm ← start with LOAEL not MADL
- Animal exposure: 6 hr/day
- Human equivalent concentration: 1.25 ppm
- LOAEL factor: 10 (as chosen in MADL analysis)
- Subchronic factor: 1
- Interspecies factor: 3
- Intraspecies factor: 3 or 10 ← possible values for pregnant workers
- Cumulative uncertainty factor: 100 or 300
- Adjust for shorter worker exposure: 20/10 x 7/5 ← may not be appropriate for developmental toxicants
- Example health-based occupational air concentrations: 0.01, 0.04 ppm
Summary of Example Health-Based Occupational Air Concentrations ($C_{occ}$) for Benzene

<table>
<thead>
<tr>
<th>Basis for Example $C_{occ}$</th>
<th>Example $C_{occ}$ (ppm)</th>
</tr>
</thead>
</table>
| Hematological effects in refinery workers (cREL) | 0.5  
|                               | 0.2  
|                               | 0.05 |
| Hematological effects in factory workers (RfC) | 0.2  
|                                               | 0.07 |
|                                               | 0.02 |
| Hematological effects in neonates (MADL)     | 0.04  
|                                              | 0.01  |
| 1 in 1,000 cancer risk*                    | 0.05  |

*Current Cal/OSHA PEL: 1 ppm (includes feasibility)*

*Current ACGIH TLV: 0.5 ppm*

*Using OEHHA unit risk value and heavier breathing rate for workers*
Concluding Remarks

- Screening level assessments can be used to identify priorities for further evaluation
- OEHHA and U.S. EPA risk assessments can be adjusted and applied to the workplace, leveraging scarce resources
- Evaluating risk assessments for application to the occupational setting must be done by a qualified expert
  - Can’t apply formulas; need to consider potentially complicating factors
- Health-based occupational levels can:
  - Be developed using a transparent, scientific, risk-based approach; and
  - Provide richer information to stakeholders and useful guidance to risk managers
- Technical and economic feasibility can still be taken into account by risk managers in setting exposure limits
For More Information

- OEHHA web site:
  www.oehha.ca.gov

- Proposition 65:
  http://www.oehha.ca.gov/prop65.html

- OEHHA guidance on developing cancer potencies and unit risk values (being updated):

- OEHHA guidance on developing chronic reference exposure levels (being updated):
  http://www.oehha.ca.gov/air/chronic_rels/pdf/relsP32k.pdf