Occupational Health Hazard Risk Assessment Project for California

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Presentation at Cal/OSHA Public Advisory Meeting
April 4, 2008

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

Under-Regulated Reproductive/ Developmental Toxicants

- 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 $\mu g/m^3$) of a given chemical

- The hexachlorobenzene unit risk value can be understood most simply as follows:

  If 10,000 people inhaled 1 $\mu g/m^3$ 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:

$$\text{Risk} = \underbrace{0.00051(\mu g/m^3)^{-1}}_{\text{Unit Risk}} \times \underbrace{2\,\mu g/m^3}_{\text{PEL}} \times \underbrace{\frac{10}{20} \times \frac{5}{7} \times \frac{50}{52} \times \frac{40}{70}}_{\text{Worker Exposure Factors}} = 2 \times 10^{-4}$$

- 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:

$$\text{Risk} = 0.049\ (\text{mg/m}^3)^{-1} \times 5\ \text{mg/m}^3 \times \frac{10}{20} \times \frac{5}{7} \times \frac{50}{52} \times \frac{40}{70} = 5 \times 10^{-2}$$

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

$$C_{occ} = \frac{0.001}{0.049\ (\text{mg/m}^3)^{-1}} \times \frac{20}{10} \times \frac{7}{5} \times \frac{52}{50} \times \frac{70}{40} = 0.1\ \text{mg/m}^3$$

1 in 1000 Cancer Risk

Unit Risk

Worker Exposure Factors

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

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

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

Noncancer Risk Assessment Basics (cont.)

- 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

Basis for Example C_{occ}	**Example C_{occ} (ppm)**
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*):
  http://www.oehha.ca.gov/air/hot_spots/pdf/May2005Hotspots.pdf
- OEHHA guidance on developing chronic reference exposure levels (*being updated*):
  http://www.oehha.ca.gov/air/chronic_rels/pdf/relsP32k.pdf