Setting Surface Limits (TLV-SLs)

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Outline

- Basic concepts for setting surface limits
- Case Study 1: Setting a surface limit based on the TLV-TWA
- Case Study 2: Setting a surface limit based on the TLV-STEL
- Case Study 3: Setting a surface limit based on study data
- Case Study 4: Setting a surface limit for a dermal sensitizer
- Summary

Surface Limits (TLV-SL®) – Basic Concepts

- Dermal exposure is associated with a large number of work-related illnesses.
- Historically, Skin and Sensitizer notations have been used to highlight chemical-specific hazards following dermal exposure.
- Some examples:

NIOSH

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Surface Limits (TLV-SL®) – Basic Concepts

- There are very few chemical substances with surface limits established, required or implied.
- Lead, Chromium (target levels)
- Beryllium (US DOE)
- Pesticides (US EPA)

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Surface Limits (TLV-SL®) – Basic Concepts

- TLV-SL® = the concentration on workplace equipment and facility surfaces that is not likely to result in adverse effects following direct or indirect contact.
- Is intended to supplement to airborne TLVs®, especially for substances with Skin, DSEN, and/or RSEN notations, and A1 and A2 Carcinogen Categories.
- Intended to protect against systemic toxicity, sensitization, and cancer from contact with contaminated work surfaces.
- Examples of recent TLV-SLs
  - o-phthalaldehyde (2019), methyltetrahydrophthalic anhydride isomers (2019), benzoquinone (2022 NIC), ethylene glycol dinitrate (2022 NIC), methylnaphthalene, all isomers (2022 NIC), propylene glycol dinitrate (2022 NIC)

Why Measure Surface Exposures?

- Preliminary risk assessment
- Routine surveillance (*e.g.*, USP 800 for hazardous drugs)
- Intervention evaluation
- Identify determinants of exposure
- Education
- Compliance monitoring

Surface Limits (TLV-SL®) – Basic Concepts

- Workplace activities can generate dusts/aerosols which may deposit on equipment surfaces. Leaks and splashes with liquids can also occur.
- Visual limits on contaminated surfaces 100-500 µg/100 cm^2.
- Chemicals can be present on surfaces below limits of visibility but may still represent toxicologically significant amounts.
- Direct contact with “contaminated” equipment → chemical transfer from surface to (exposed) skin.
- The amount of systemic absorption of chemicals from skin into the blood is influenced by various physico-chemical and exposure-related factors.

Setting a TLV-SL: Starts with the Dose

- For systemic effects: from a specific dermal study or the same dose used to develop the TLV-TWA.
  - TLV-TWA is an acceptable daily exposure (ADE) or "safe" level of exposure divided by the volume breathed in 8 hours (10 m^3).
  - "Occupational ADE" (ADE_{occ}) = TWA (ug/m^3) * 10 m^3
- ADE_{occ} divided by standard surface area (100 cm^2)
- Adjustments are made for differences in bioavailability (e.g., oral vs. dermal, inhalation vs. dermal, dermal vs. dermal).

Kimmel et al. 2011

Setting a TLV-SL: Uncertainties/Limitations

- What is the exposure “scenario?”
  - One contact per day, 100 cm^2?
- Will transfer from surface to skin be complete?
  - Some substances may be retained on equipment surface
- Is the contacted skin healthy?
  - Diseased or damaged skin → higher absorption (dose)
- Should the uncertainty factor address these issues?
- How much of this should be addressed by the exposure evaluation and risk assessment? Need to know the assumptions.

Setting a TLV-SL: Dermal Absorption Potential

- Physico-chemical properties (e.g., OECD, 2011)
  - MW < 500 Da
  - Log K_{ow} between -1 and +4
  - If both criteria are met: 100% absorption
  - If both criteria are not met: 10% absorption
- Compound-specific dermal absorption data are preferred.
- Need to account for the difference in absorption between the dermal route in workers and the point-of-departure (PoD) route.
- Effects in animal/human oral/inhalation vs. dermal studies.

Setting a TLV-SL: Basic Calculation

$$\text{TLV-SL} = \frac{ADE_{occ}}{(100\ cm^2)\ (\alpha)}$$

Where:

ADE_{occ} = Occupational ADE

α = bioavailability adjustment factor to account for the difference in absorption between the dermal route in workers and the point-of-departure (PoD) route (F_{Dermal})/F_{PoD}).

Case 1: Setting a TLV-SL using the TLV-TWA (hypothetical example)

TLV-TWA = 0.5 µg/m^3

ADE_{occ} = 0.5 µg/m^3 * 10 m^3 = 5 µg

α = 0.1 (10%/100%)

$$\text{TLV-SL} = \frac{5\ \mu g}{(100\ cm^2)(0.1)}$$

TLV-SL = 50 µg/100 cm^2

Setting a TLV-SL Without a TLV

- Map occupational exposure banding (OEB) system to TLV-SL values
  - More arbitrary, may not be appropriately conservative.
- Convert ADE (OEL, RfD, TDI, etc.) to ADE_{occ}
  - Must account for differences in bioavailability by various routes, interspecies differences, levels of risk between human subjects and workers, human subject versus worker demographics.
- Use caution – critical effect (PoD) might be different with dermal exposure.

Occupational Exposure Band

1 2 3 4 5

Occupational Exposure Limit

>1 mg/m^3	1 mg/m^3	100 μg/m^3	10 μg/m^3	1 μg/m^3	<1 μg/m^3

Visible Dust – General Cleanliness Requirements	1 mg/100 cm^2	100 μg/100 cm^2	10 μg/100 cm^2	<10 μg/100 cm^2

Surface Limit

Adapted from Naumann et al. 1996

Case 2: Setting a TLV-SL using the TLV-STEL

Ethylene glycol dinitrate (NIC 2022)

TLV-STEL 0.01 ppm, Skin

TLV-SL 0.02 mg/100 cm^2

TLV Basis: Headache; hypotension; cerebrovascular & cardiovascular disease; vasodilation

Case 2: Setting a TLV-SL using the TLV-STEL

The TLV-SL was calculated using a method described by Kimmel et al (2011) and the dose allowed during 15 minutes of exposure at the STEL of 0.01 ppm (0.0622 mg/m^3).

Over 15 minutes, an average healthy worker inhales 0.3125 m^3 of air. Therefore 0.0622 mg/m^3 x 0.3125 m^3 = 0.01944 mg (rounded up to 0.02 mg).

Dividing this number by 100 cm^2, corresponding to the surface area of the palm of 1 hand, yields 0.02 mg/100 cm^2.

Case 2: Setting a TLV-SL using the TLV-STEL

TLV-STEL = 0.01 ppm = 0.0622 mg/m^3

ADE_{occ} = 0.0622 mg/m^3 * 0.325 m^3 = 0.02 mg

α = 1 (100%/100%)

$$\text{TLV-SL} = \frac{0.02 \text{ mg}}{(100 \text{ cm}^2)\ (1)}$$

TLV-SL = 20 µg/100 cm^2

Case 3: Setting a TLV-SL using study data

Phenylethyl Alcohol (NIC 2022)

TLV-TWA, 0.5 ppm, Skin

Considered setting a TLV-SL

TLV Basis: Embryo/fetal damage

Case 3: Setting a TLV-SL using study data

Phenylethyl Alcohol (PEA) Draft *Documentation*

PEA uptake through human skin (N=2) appears to be relatively low (7.6%) compared to uptake through rat skin (77%) and rabbit skin (50%).

However, human absorption was likely underestimated due to evaporation from the skin in the dermal absorption study.

PEA produced developmental toxicity in rats at low dermal dosages (LOAEL=70 mg/kg in dermal rat study).

Case 3: Setting a TLV-SL using study data

Phenylethyl Alcohol (PEA) produced developmental toxicity in a dermal study in rats with a LOAEL = 70 mg/kg x 70 kg = 4900 mg.

ADE_{Occ} = 4900 mg/(150 x (1/0.77)) = 25 mg/day with α = 1.3

If human dermal absorption data are applied, α = 0.1 (7.6%/77%)

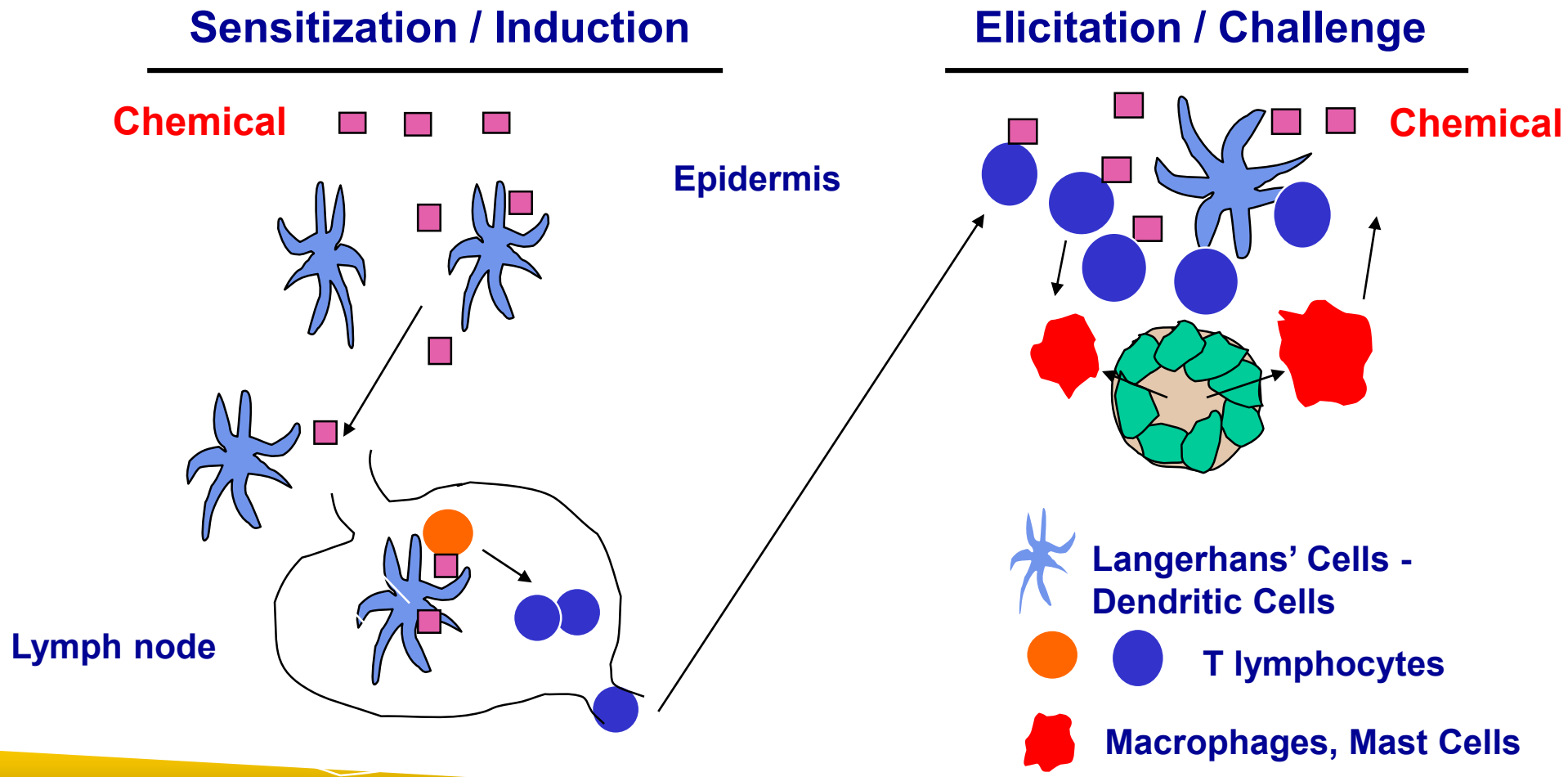
$$\text{TLV-SL} = \frac{25\ \text{mg}}{(100\ \text{cm}^2)\ (0.1)} = 250\ \text{mg}/100\ \text{cm}^2$$

Considering this high level (well above the visual threshold) and the high vapor pressure which will result in significant evaporation, it was decided not to recommend a TLV-SL for PEA.

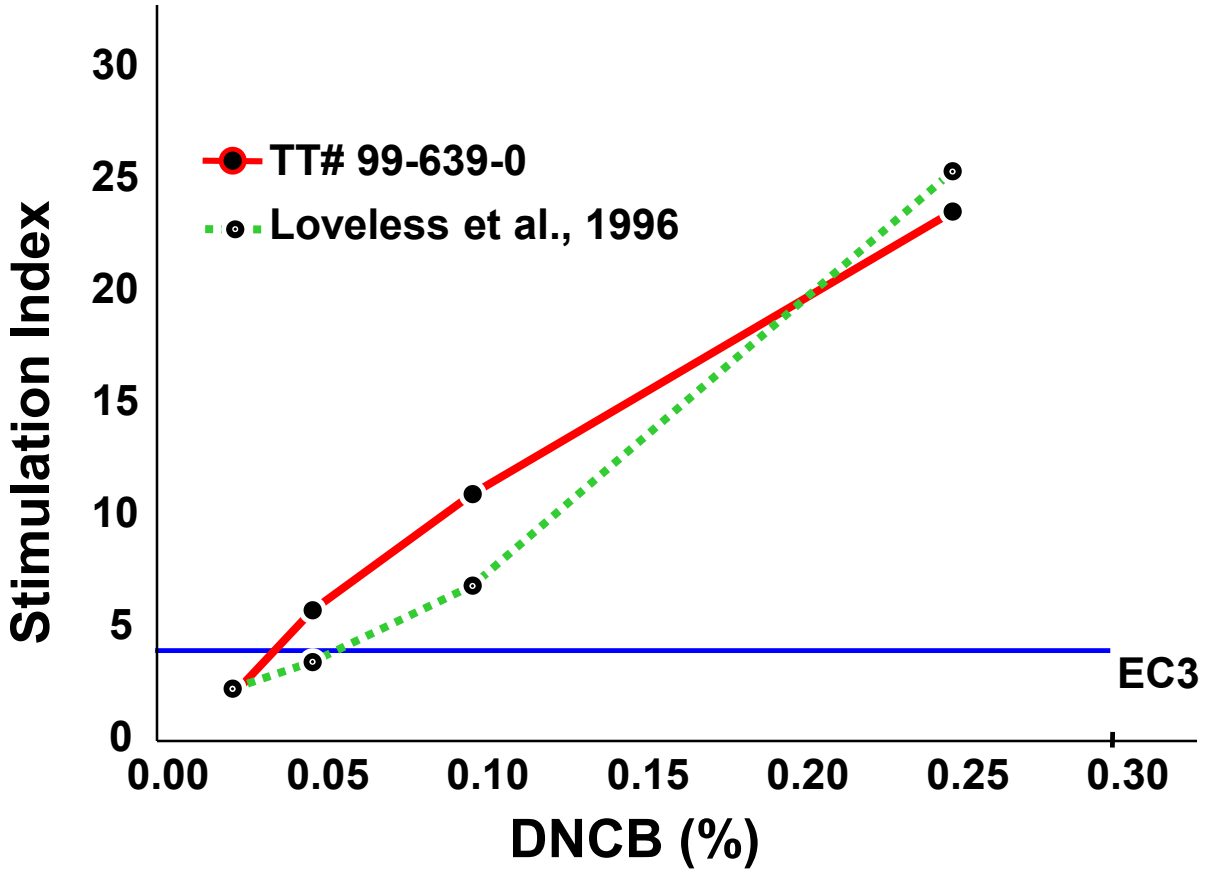
Case Study 4: Setting a TLV-SL for a skin sensitizer

- Sensitization is a significant concern for workers.
- The LLNA is used to identify skin sensitizers.
- Can calculate a surface limit using the LLNA EC3 value.
- LLNA EC3/HRIPT NOEL Ratios inform Adjustment Factors.
- Risk Assessment/Management: How to maintain safe levels in the workplace for skin sensitizers.

Mechanism of Contact Hypersensitivity
(Type IV Cell-Mediated vs. Type I IgE-Mediated)



Murine Local Lymph Node Assay (LLNA) Results: Dinitrochlorobenzene



EC3 – Effective concentration corresponding to a 3-fold increase in lymphocyte proliferation above controls

LLNA EC3/HRIPT NOEL Ratios

Compound	HRIPT NOEL (ug/cm^2)		LLNA EC3 (ug/cm^2)	LLNA/HRIPT* Ratio
Methylchloroisothiazolinone/ Methylisothiazolinone	1	**Strong**	2.5	2.5
2,4-Dinitrochlorobenzene	8.8		20	2.3
p-Phenylenediamine	10		15	1.5
Formaldehyde	37		162	4.4
Isoeugenol	69	**Moderate**	450	6.5
Glutaraldehyde	100		23	0.2
Cinnamic aldehyde	591		500	0.8
Citral	775		3250	4.2
Eugenol	1938	**Weak**	2225	1.1
Hydroxycitronellal	2953		5000	1.7

* LLNA - Local lymph node assay, HRIPT – Human repeat insult patch test

From Gerberick et al. 2001

Using the LLNA EC3 to Derive Surface Limits

Default Adjustment Factor (AF_C = 50)

AF_R = 6 (EC3/HRIPT Ratio Variability)

AF_M = 3 (Matrix Considerations)

AF_E = 3 (Exposure Considerations)

MF = 1 (Low-to-moderate sensitizer)*

***Consider MF = 2 (Strong sensitizer) or MF = 3 (Extreme sensitizer)**

From Naumann and Arnold (2019)

Using the LLNA EC3 to Derive Surface Limits

Example: o-Phthalaldehyde (25 μl applied to 1 cm^2)

EC3 = 0.051% = 510 μg/ml x 0.025 ml ÷ 1 cm^2 = 13 μg/cm^2

Surface Limit Derivation:

Surface Limit = (EC3 (μg/cm^2) ÷ Adjustment Factor) x 100

Surface Limit = (13 μg/cm^2 ÷ 50) x 100 = 25 μg/100 cm^2

Note: Surface area of the palm of one hand is approximately 100 cm^2.
This is also the standard surface area for wipe sampling.

From Naumann and Arnold (2019)

Using the LLNA EC3 to Derive Surface Limits

Compound	CAS Number	LLNA Potency Classification	LLNA EC3 (% w/v)	Surface Limit
Oxazolone	15646-46-5	Extreme	0.01	1 ug/100 cm^2
Dinitrochlorobenzene	97-00-7	Extreme	0.08	10 ug/100 cm^2
p-Phenylenediamine	106-50-3	Extreme	0.09	10 ug/100 cm^2
Glutaraldehyde	111-30-8	Strong	0.20	50 ug/100 cm^2
Trimellitic Anhydride	552-30-7	Strong	0.22	60 ug/100 cm^2
Phthalic Anhydride	85-44-9	Strong	0.36	90 ug/100 cm^2
Formaldehyde	50-00-0	Strong	0.40	100 ug/100 cm^2
Diethylmaleate	141-05-9	Moderate	2.1	1050 ug/100 cm^2
Phenylacetaldehyde	122-78-1	Moderate	4.7	2350 ug/100 cm^2
Citral	5392-40-5	Weak	13	6500 ug/100 cm^2
Diethanolamine	111-42-4	Weak	40	20000 ug/100 cm^2

Adapted from Kimber et al. 2003

Risk Assessment/Risk Management

How to maintain safe exposure levels in the workplace for a skin sensitizer:

- **Assign** DSEN Notation, OEB, **Update** SDSs/Labels (awareness helps).
- **Design** appropriate engineering controls.
  - For strong sensitizers, additional engineering controls and PPE may be needed.
  - For weak-to-moderate sensitizers, special containment equipment may not be necessary.
- **Establish** good chemical handling practices.
- **Use** appropriate protective equipment to minimize contact (e.g., gloves, sleevelets, lab coat, coveralls, full-face respirator).
- **Set** surface limits, **conduct** monitoring and **verify** effectiveness of exposure controls.

Summary – Surface Limits

- A TLV-SL is a “safe” level of (in)direct contact exposure to chemicals deposited on workplace/facility surfaces that provides an objective benchmark.
- A TLV-SL can be set using study specific data or can be extrapolated from the TLV-TWA or TLV-STEL. Need to consider bioavailability differences.
- A TLV-SL based on the LLNA EC3/HRIPT NOEL ratio reflects both intra-species and inter-species differences; however, additional adjustment factors may be appropriate to address vehicle/matrix and exposure considerations.

Summary – Surface Limits

- TLV-SLs are intended to supplement airborne TLVs and to provide quantitative criteria for establishing acceptable surface concentrations.
- TLV-SLs should be part of comprehensive risk assessment and mitigation process.
- Always review the TLV - *Documentation* for the contaminant.
- Understand the relationship between the assumptions that go into setting the TLV-SL and the exposure evaluation.

References

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