Deriving Protective OEBs and OELs for OTC Drugs

Accounting for Pharmacological Effects

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Agenda

- Background of case study
  - Defining the problem (case study overview)
  - SDSs for OTC drugs
  - Overview of OELs and OEBs
- Pharmacology & Toxicology
- GHS Limitations
- Case Study Calculations
- Key Take-Aways

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The Background

The Case study
Understanding of Exposure Limits

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Scope of Work (background)

- Client has an Over the Counter (OTC) product with the Active Pharmaceutical Ingredient (API) "*alpha*" with a reports from a national firms developing a SDS and assessing the OEB.
- Additional pharmacologic data were produced since this report.
- The deliverable was to produce an OEL & OEB for manufacturing and be able to defend it.

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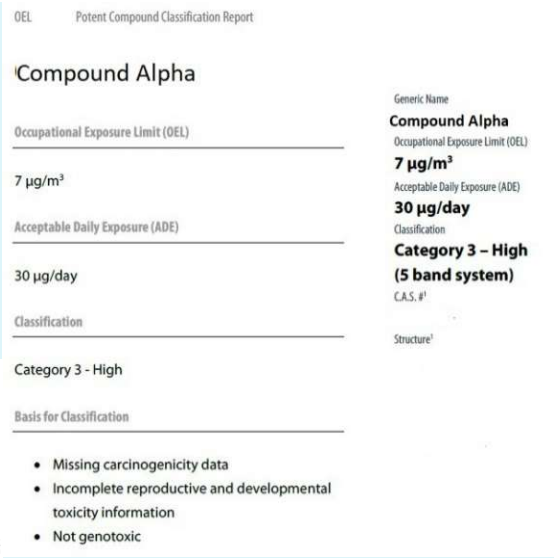
Case Study (hurdles)

- Conflicting reports.
- Decoding a ~2,000 page toxicology study.
- Determining a defensible OEL.



OEL Potent Compound Classification Report

Compound Alpha

Occupational Exposure Limit (OEL)

7 µg/m³

Acceptable Daily Exposure (ADE)

30 µg/day

Classification

Category 3 - High

Basis for Classification

- Missing carcinogenicity data
- Incomplete reproductive and developmental toxicity information
- Not genotoxic

Generic Name

Compound Alpha

Occupational Exposure Limit (OEL)

7 µg/m³

Acceptable Daily Exposure (ADE)

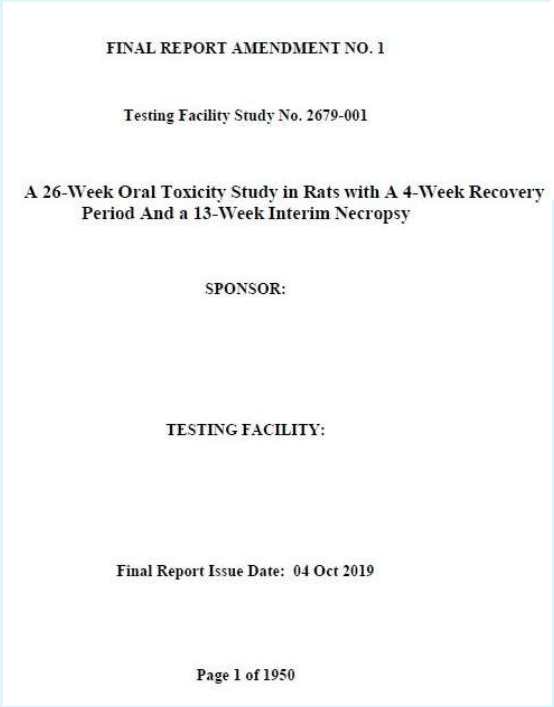
30 µg/day

Classification

Category 3 – High (5 band system)

C.A.S.#[1]

Structure[1]



FINAL REPORT AMENDMENT NO. 1

Testing Facility Study No. 2679-001

A 26-Week Oral Toxicity Study in Rats with A 4-Week Recovery Period And a 13-Week Interim Necropsy

SPONSOR:

TESTING FACILITY:

Final Report Issue Date: 04 Oct 2019

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Reconciling Toxicology and Pharmacology for an OEL

Toxicology

- Little or no manipulation; it plugs directly into the standardized GHS hazard algorithms.
- Exposure limits are not universally calculated.*

Pharmacology

- Pharmacological Data is Built for Healing: Clinical trial data measures therapeutic efficacy.

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**methods A & B will be discussed later.*

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The Translation Gap

A worker inhaling powder in a factory isn't a patient seeking treatment. To use clinical pharmacological data for an SDS, you have to mathematically work backward.

You aren't just dividing numbers to prevent *damage* (toxicity); you are applying massive safety factors (like our 100x buffer) to strip away the drug's *action*.

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Translating Pharmacology Data

- Creating SDSs from pharmacological data requires that efficacy data be translated into hazard data.
- How well an API works to achieve its desired function under controlled testing does directly give data to protect “workers” from biologically active materials.

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SDSs and FDA Regulated OTC Drugs

OSHA typically regulates

- Manufacturing of the API
- Formulations and compounding
- Patient delivery

OSHA typically does *not* regulate:

- OTC pharmaceuticals in patient ready format

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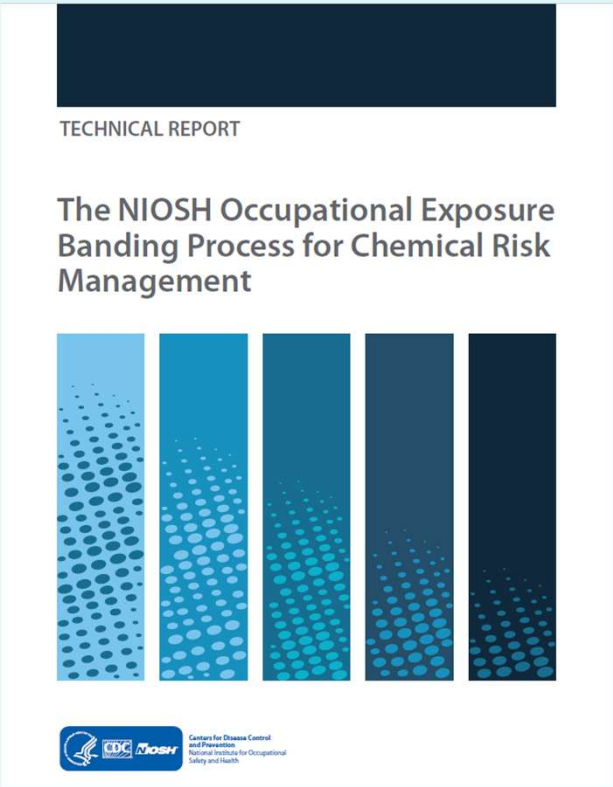
Overview OEL vs. OEB



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Occupational Exposure Banding (OEB) & NIOSH Tiers

What it is

A *qualitative* or *semi-quantitative* risk management strategy that categorizes chemicals into specific "bands" (e.g., A–E) based on hazard severity and exposure potential

How it is used

When no OEL exists, the band dictates the required engineering controls — from general ventilation for Band A to strict containment for Band E.

The Tier 3 Connection

While Tiers 1 and 2 rely on standard GHS codes, Tier 3 uses *expert judgment* and *pharmacological data* to perform an advanced health risk assessment — generating a highly protective, chemical-specific internal limit.

Tier 3 bridges the gap between a generic band and a precise OEL.

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Occupational Exposure Limit (OEL)

classic method

What it is

A specific, *quantitative* limit on the acceptable concentration of a hazardous substance in workplace air.

How it is used

Traditional industrial hygiene relies on taking personal air samples and comparing the analytical results directly to this strict numerical limit to ensure workers do not suffer adverse health effects.

The Challenge

Establishing official OELs requires extensive toxicological data, time, and resources.

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Occupational Exposure Limit (OEL)

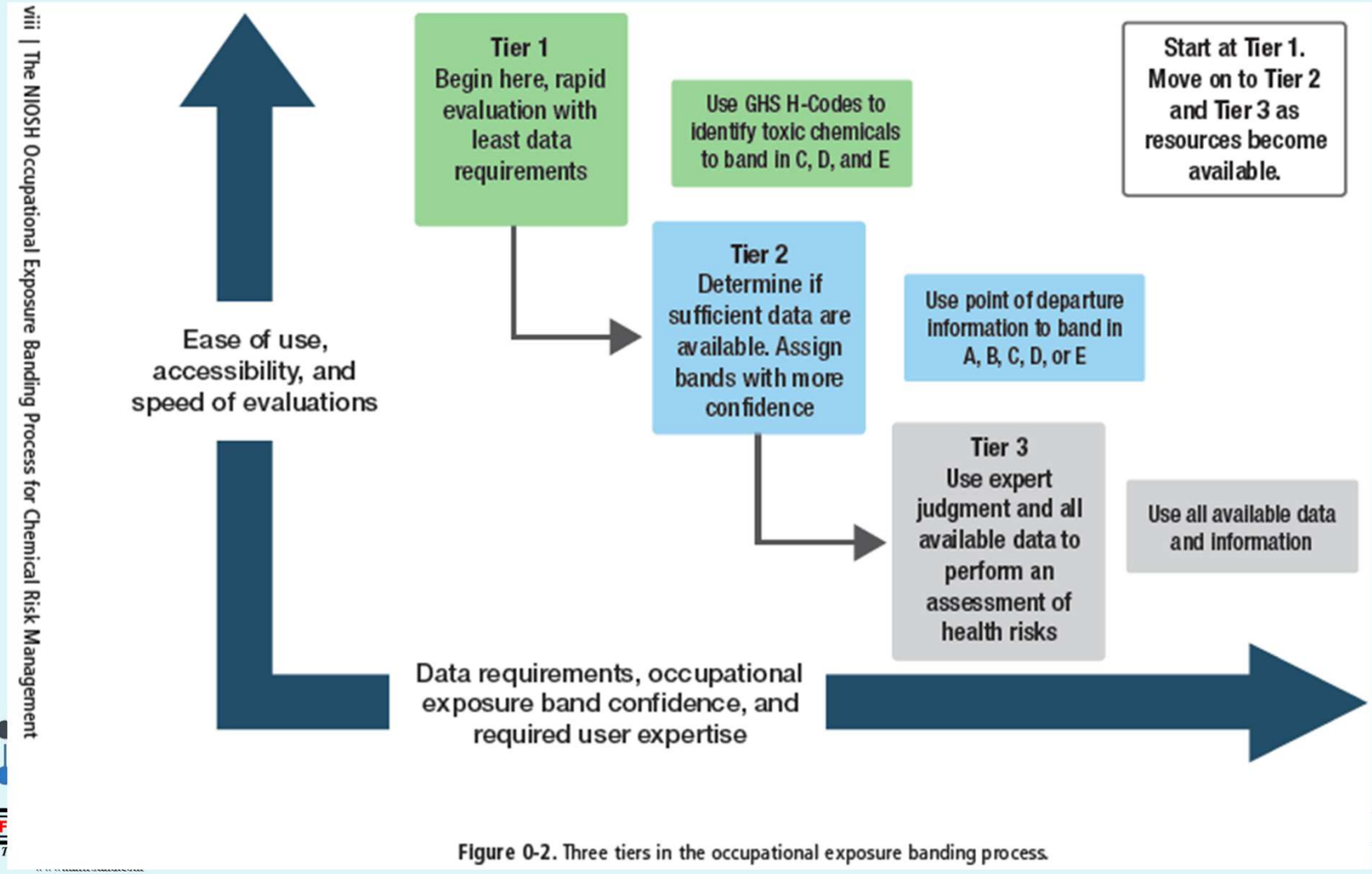

Figure 0-2. Three tiers in the occupational exposure banding process.

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Determining Exposure Limits

- No one agreed upon method.
- Often uses epidemiological data or real-world events.
- There are two recognized methods for using toxicology study data A&B.

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Exposure Limits Calculations

- Which method chosen may be subjective.
- Safety factors are subjective.
- Why choose A vs. B?

- Which is Defensible

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OEL Calculations: Method A vs. Method B

Method A — Animal Toxicity Driven

You use this method when:

- **The Chemical is New or Unstudied:** Before a novel industrial chemical can be manufactured at scale, regulatory frameworks require animal testing to establish safety baselines.
- **Assessing Severe or Irreversible Harm:** To predict long-term health hazards like cancer, reproductive toxicity, organ failure, or genetic mutation. It is unethical to wait for or test these endpoints in humans, so animal models dictate the Occupational Exposure Level (OEL).
- **No Reliable Human Data Exists:** For the vast majority of the tens of thousands of chemicals used in manufacturing, human exposure data is either poorly tracked or entirely absent.

Method B — Human Pharmacology Driven

Human-derived data is whenever it is available and robust enough to establish a Point of Departure*.

You use this method when:

- **Evaluating Legacy Chemicals:** For chemicals that have been used heavily for decades (e.g., benzene, lead, asbestos, silica), extensive epidemiological studies on exposed workers provide real-world data that overrides animal models.
- **The Critical Effect is Mild or Sensory:** For endpoints like eye and throat irritation, dizziness, or odor thresholds. Animal models are poor predictors of these subjective effects, so controlled human volunteer studies or workplace surveys are used to set the limit.

*The highest amount of a chemical that is known not to cause harm, or the absolute lowest dose where a tiny biological effect just starts to show.

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Understanding Toxicology & Pharmacology

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Finding Harm vs. Finding Help

- **Toxicology:** Determining "how nasty" a compound is to cells and tissues — measuring damage and death, not functional biological response.
- **Pharmacology:** Determining biological activity, therapeutic efficacy, and functional physiological responses. Rather than asking "when does the organ fail?", pharmacology asks "when does the body respond?"

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Pharmacology (Harm vs. Help)

- Looks for patient benefits.
- Does not focus on looking for harmful effects.
- Not geared for healthy individuals.

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Terminology

Animal Studies

- Used in both toxicological and pharmacological studies and can be used in SDS and OEL development

Genotox studies

- Looks at breaks in DNA
- Includes mutation studies

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Toxicology Terminology (animal studies)

No-Observed-Adverse-Effect-Level (NOAEL)

- Highest experimental dose that shows no statistically *significant adverse* structural or *organ toxicity* in animal studies.

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Toxicology Terminology (Genotox)

Ames Test (Bacterial Mutation Assay)

- Tests whether a chemical mutates DNA in bacterial cultures. A *positive result indicates mutagenic potential*.

Chinese Hamster Ovary Assay (CHO)

- In vitro test detecting structural chromosomal damage in mammalian cells.

Micronucleus Assay

- In vivo red blood cell test detecting chromosome fragment damage.

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Pharmacology Terminology

Minimum Therapeutic Dose (MTD)

- The lowest clinical dose required to trigger an intended biological response in humans. Derived from clinical trial data and represents the threshold of pharmacological activity.

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Pharmacology Terminology

Acceptable Daily Exposure (ADE)

- A calculated daily dose of a substance below which adverse health effects are not expected over a lifetime. Incorporates safety factors applied to clinical and toxicological data.

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Stages in Drug Development
(pertinent to SDS/OEL development)

- Genotoxicity
- Animal Studies
- Pharmacology
- Clinical Trials

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Toxicology vs. Pharmacology

Key Distinction

- Pharmacological endpoints capture **functional effects** (nausea, receptor saturation, physiological response) that occur at doses far below those required to produce structural toxicological damage

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The Dose-Escalation Paradigm

- Toxicological study design is fundamentally about finding the breaking point. Researchers administer escalating doses until adverse effects appear — organ pathology, cellular mutation, or mortality. The NOAEL is then set just below that threshold.
- This approach is well-suited for industrial chemicals, solvents, and heavy metals — compounds where the primary hazard is *structural tissue damage*.

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The Paradigm Failure

- For pharmacologically active compounds, the "breaking point" for functional effects occurs at doses *orders of magnitude lower* than structural damage thresholds. A NOAEL derived from organ pathology data is simply the wrong endpoint for a receptor agonist.
- The genotoxicity battery — Ames, CHO, Micronucleus — evaluates DNA integrity, not receptor binding affinity or functional physiological response.

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GHS Limitations

Definitions vs. Reality

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Limits of Standard GHS Risk Classification

GHS / Standard SDS Path

Acute Toxicity

Oral LD_{50} = 101 mg/kg (Mouse) →

Acute Toxicity Category 3

Organ Toxicity

Minimal, non-adverse, and **reversible** at tested doses

Genotoxicity

Negative across Ames, Chromosome Aberration, and Micronucleus assays

SDS Outcome

Assigned to a **lenient hazard band** (e.g., Band A / No OEL)

Manufacturing Floor Reality

High-Affinity Receptor Agonist

- Substance is pharmacologically active at sub-toxic doses

Symptoms at Sub-Toxic Doses

- Nausea, emesis (vomiting), tremors, salivation, dizziness

The Conflict

- SDS protects organs against long-term failure, but allows workers to absorb active doses on shift

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The Case Study

Formulas
Calculations
Recommendations

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The Mathematical Formulas

Method A Formula

Toxicology / Animal NOAEL Approach

$$OEL = \frac{NOAEL\left[\frac{mg}{kg\ day}\right] \times Body\ Weight\ [70\ kg]}{Uncertainty\ Factors \times Breathing\ Volume\ [10\ \frac{m^3}{day}]}$$

Where Uncertainty Factors typically = **100**
(10× interspecies × 10× intraspecies)

Method B Formula

Pharmacology / Human Therapeutic Dose Approach

$$ADE = \frac{MTD\left[\frac{mg}{day}\right]}{Safety\ Factors\ (SF)}$$

$$OEL = \frac{ADE\left[\frac{mg}{day}\right]}{Breathing\ Volume\ [10\ \frac{m^3}{day}]}$$

Where SF is a composite of pharmacokinetic and pharmacodynamic adjustment factors

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Comparison of the Formulas

PoD Units Differ

Method A: mg/kg/day (animal dose normalized to body weight).

Method B: mg/day (human clinical daily dose — no species conversion needed).

Breathing Volume Constant

Both methods use **10 m^3/day** as the standard occupational breathing volume for an 8-hour TWA calculation.

ADE as Intermediate

Method B introduces the Acceptable Daily Exposure (ADE) as an intermediate value — the maximum daily systemic dose considered safe for a worker.

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Comparison of A vs. B

Method A — Animal Toxicity Driven

Point of Departure: Animal NOAEL (No Observed Adverse Effect Level)

Objective: Prevent systemic organ damage in workers

Appropriate for: Industrial chemicals without specific target-receptor activity

- Relies on interspecies extrapolation
- Standard uncertainty factors: 10× interspecies, 10× intraspecies
- Does not account for pharmacological potency at sub-toxic doses

Method B — Human Pharmacology Driven

Point of Departure: Minimum Therapeutic Dose (MTD) from human clinical data

Objective: Keep worker absorption of **<1% of a clinical therapeutic dose**

Appropriate for: Active compounds, biologicals, and receptor agonists/antagonists

- Anchored directly to human pharmacokinetic data
- Eliminates interspecies uncertainty by using human clinical evidence
- Protects against functional pharmacological effects, not just organ toxicity

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Method A Calculations (case study)

Method A: Calculation based on Animal Toxicity (Chronic Dog Study)

Rationale: Using the dog NOAEL (2 mg/kg/day) because the dog was the most sensitive species regarding clinical signs like emesis.

- **Point of Departure (NOAEL):** 2 mg/kg/day.
- Calculation:

$$OEL = \frac{NOAEL \times BW}{UF_{composite} \times V}$$

  - *(Human Body Weight): 70 kg*
  - *V (Breathing Volume):* 10 m^3 (Standard 8-hour shift)
  - *UF (Uncertainty Factors):*
    - 10 (Interspecies extrapolation: Dog to Human)
    - 10 (Intraspecies variability: Sensitive workers)
    - Total UF = 100.

$$OEL = \frac{2 \times 70}{100 \times 10} = 0.14 mg/m^3 \text{ or } 140 \mu g/m^3$$

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Method B Calculations (case study)

Method B: Calculation based on Human Therapeutic Dose (Pharmacology)

Rationale: This is the industry standard for APIs. This is used to calculate an OEL that prevents pharmacological effects in workers.

- **Minimal Therapeutic Dose (MTD):** 3 mg (Single tablet dose).
- **Safety Factor (SF):** 100.
  - *Rationale:* This composite factor accounts for intraspecies variability (10x) and extrapolating from a Lowest-Observed-Effect-Level (LOEL) to a No-Effect-Level (10x). This ensures the worker absorbs <1% of the therapeutic dose.
- Calculation:

  ADE (Acceptable Daily Exposure) = 3.0 mg/100 = 0.03 mg/day

  OEL ADE/V = 0.03 mg/10 m^3 = 0.003 mg/m^3
- **Result: 3.0 µg/m^3**

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Method A Analysis: OEL = 140µg/m³

Animal NOAEL Inputs

- Animal NOAEL = **2 mg/kg/day** (Dog 39-Week Study)
- Uncertainty Factors (UF) = **100** (10× Interspecies, 10× Intraspecies)
- Body Weight = 70 kg | Breathing Volume = 10 m³/day

$$OEL = \frac{2 \times 70}{100 \times 10} = 0.14 mg/m^3 \text{ or } 140 \mu g/m^3$$

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Method B Analysis OEL = 3µg/m³

METHOD B — PHARMACOLOGY

Human Clinical Inputs

- Human Minimal Therapeutic Dose (MTD) = **3.0 mg/day**
- Safety Factor (SF) = **100** (10× Intraspecies, 10× LOEL-to-NOEL)
- ADE = 3.0 / 100 = **0.03 mg/day**

$$\text{OEL} = \frac{0.03\,mg}{10\,m^3} = 0.003\,\frac{mg}{m^3} = \mathbf{3\,\mu g/m^3}$$

Validated Protection: At 3 µg/m³, a worker inhales **0.03 mg/day** — **<1% of the therapeutic dose**. Completely protective against pharmacological effects.

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Method A Analysis

⊗ **Critical Failure:** At 140 µg/m³, a worker inhales **1.4 mg/day** — approximately **15% of a therapeutic dose** — causing nausea and emesis on shift. This OEL is not protective for a pharmacologically active compound.

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Banding Comparison

Parameter	Method A	Method B
Calculated OEL	140 µg/m³	3 µg/m³
OEB Classification	Band 3 (Moderate)	**Band 4 (Highly Potent)**
Handling Regime	Local exhaust ventilation, open handling permitted	**Closed systems mandatory**
Worker Protection	Inadequate — 15% dose absorbed	**Adequate — <1% dose absorbed**

Method A places Compound Alpha in **Band 3**, permitting open handling with local exhaust ventilation — a regime that exposes workers to acute pharmacological effects. Method B correctly classifies it as **Band 4**, mandating closed-system engineering controls.

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Final OEB Banding & SDS Section 8 Recommendations

Internal OEL

3 µg/m³ (8-hour TWA) — Override GHS software default. Do not use Method A value.

Occupational Exposure Band

Band 4 — Highly Potent Hazard (Range: 1–10 µg/m³). Explicitly state pharmacological basis.

Mandated Engineering Controls

Closed systems required: vacuum transfer, split butterfly valves, isolators. No open weighing or dispensing.

Handling Guidance Language

Avoid dust generation. Material is **pharmacologically active at low doses**. Inhalation exposure may cause acute clinical effects below traditional toxicological thresholds.

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Previous Report Responses

- Original report assumed “worse case scenario” for missing data.
- New data were generated after original report.
- Original report used a factor of only 3 to extrapolate from the therapeutic dose to a No Observed Effect Level (NOEL), and a factor of 5 for human variability. (The industry standard for highly potent Active Pharmaceutical Ingredients (APIs) is to use a factor of 10 for each (a composite of 100).)

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Key Take-Aways

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The Challenge of Applying Pharmacological Data to an SDS

GHS Classification Absence

GHS has standard criteria for carcinogens and organ toxins, but **lacks a specific classification for 'potent receptor binding without organ damage.'** There is no GHS hazard category that captures pharmacological activity as a standalone hazard — leaving SDS authors without a regulatory hook to justify protective limits.

Over-Reliance on LD_{50}

GHS acute toxicity thresholds default to broad bands that **ignore low-dose pharmacological activity.** An LD_{50} of 101 mg/kg places a compound in Category 3 — but says nothing about receptor binding at 0.001 mg/kg. The metric is simply the wrong tool for the job.

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The Challenge of Applying Pharmacological Data to an SDS

Misleading Safety Profiles

An SDS reading *'Non-mutagenic; NOAEL = 2 mg/kg'* gives a **false sense of security, leading to open handling.** Industrial hygienists and safety professionals reading this profile have no indication that the compound is a potent receptor agonist with functional effects at sub-microgram doses.

The solution is not to abandon GHS — it is to supplement GHS classification with pharmacologically derived OELs and OEBs that capture the full hazard profile of bioactive compounds.

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Key Takeaways

As hazard communicators, we must look beyond organ toxicity.
By utilizing pharmacological data as our Point of Departure, we create truly protective SDSs that safeguard workers against both long-term injury and immediate functional illness.

The Core Principle

A worker handling a pharmacologically active compound is, in effect, a patient receiving an uncontrolled dose. The OEL must reflect that reality — not just the dose that damages an organ in a dog study.

The Compound Alpha Verdict

Method A: **140 µg/m³** → Band 3 → Worker ill on shift

Method B: **3 µg/m³** → Band 4 → Worker fully protected

- The 47× difference in stringency is not a rounding error.
- It is the difference between a compliant SDS and a protective one.

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Key Takeaways

1. **Recognize NOAEL Limits**
   Animal toxicity data alone **cannot protect workers** from potent bioactive chemicals. A NOAEL-derived OEL may permit pharmacologically significant inhalation doses that cause acute clinical effects on shift — as demonstrated by Compound Alpha's 140 µg/m³ failure case.

2. **Use Pharmacology as a PoD**
   When human clinical or receptor binding data is available, calculate OELs to keep worker absorption **<1% of the active dose**. The MTD-anchored Method B approach eliminates interspecies uncertainty and directly reflects human pharmacokinetic reality.

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Key Takeaways

3. **Cross-Industry Value**
   Apply this pharmaceutical risk assessment method across **biotech, ag-chem, specialty chemicals, and nutraceuticals**. Any compound with receptor-mediated activity or defined human pharmacological data is a candidate for Method B derivation.

4. **Drive Defensive SDS Section 8**
   Override standard GHS software defaults to enforce Band 4 controls when pharmacological potency demands it. The SDS must explicitly state the pharmacological basis for the OEL and mandate closed-system engineering controls — not merely recommend them.

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