# Control Banding

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# SafeBridge Consultants, Inc.

- Group of environmental, health and safety professionals with expertise in:
  - toxicology
  - safety
  - occupational hygiene
  - analytical chemistry
  - occupational medicine
  - developing programs to recognise, evaluate and control occupational exposures to potent pharmaceuticals
- Expertise is in pharmaceutical safety and health consulting (150 person-years experience)
  - Offices in SF Bay Area, New York City & Europe (Liverpool, UK)

# Handling Pharmaceutical Compounds is a RISKY business!

- Handling potent pharmaceuticals is a risky business
- Consequences of mishandling can be severe
- There are no SENSORS to measure for potent compounds
- Contrast extensive product quality data versus often limited or no exposure control data – Why?

# What is Control Banding?

- A means to group materials by their HAZARD and RISK OF EXPOSURE so that suitable CONTROL can be defined and applied
- In pharma, Pharmaceutical Safety Group volunteers came up with the concept, based partly on NIH/CDC Biosafety Level model
- Application has been tried for regular hazardous chemicals such as in the COSHH Essentials tool
- REACH and RiskMAPP

# Hazard

- Occupational hazard to health
- An intrinsic property of a material
- The toxicological risk that a material presents if you are exposed to it

# Where do you get Hazard Information?

- The Safety Data Sheet (SDS)
  - R and S phrases in the past
  - H and P phrases now
- The Regulator
- The supplier!
- A Toxicologist

# Examples of OELs

| Drug/Material | OEL |
|---|---|
| Hydrogen cyanide ([STEL]) | 11,200 μg/m³ |
| Naproxen (NSAID) | 5,000 μg/m³ |
| Chlorine | 1,500 μg/m³ |
| Nicardipine (cardiac drug) | 400 μg/m³ |
| Phosgene | 80 μg/m³ |
| Cyclosporin A (transplant rejection) | 20 μg/m³ |
| Paclitaxel (anti-cancer) | 0.8 – 10 μg/m³ |
| Fentanyl (synthetic opiod) | 0.7 μg/m³ |
| Thalidomide | 0.5 μg/m³ |
| Ethinyl estradiol (synthetic estrogen) | 0.035 μg/m³ |
| Nafarelin (peptide hormone) | 0.001 μg/m³ |

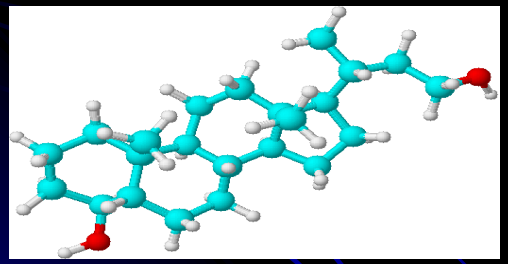
# Risk of Exposure

- Quantity handled
- Physical form
  - Liquid
  - Solid
- Physico-chemical properties
  - Crunchy crystalline or fly-away fluffy!?
  - Static?
- Transport mechanisms (mass transport drivers)

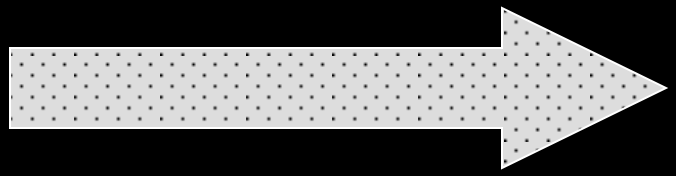
# Routes of Occupational Exposure

1. Inhalation
2. Dermal Absorption
3. Ingestion
4. Inadvertent Contact with Skin & Mucous Membranes

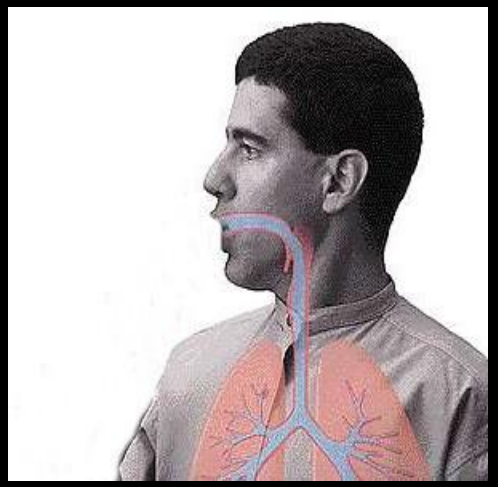
# Exposure Pathways
# Source – Pathway – Target

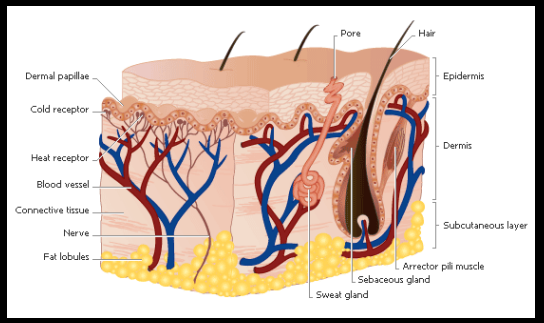


**Source**



**Pathway**






**Target**

**“MASS TRANSPORT”**

# Early Stage Compounds

- Discovery, pre-Clinical, early Clinic
- Limited information known early on, but we still need to know the hazard potential
- No data from regulators
- SDS vs NDDS
- The hazard can change as the drug substance progresses along its development timeline

# Most Critical Data for Determining which Category or “Band”

- Anticipated mechanism of action
- Anticipated or current therapeutic indication
- Anticipated or current dose
- Toxicology data – critical endpoints are “-gens”
- Drugs that may be comparable – similar structure or mechanism of action

# Typical Criteria for a 5 Band System

| Criterion | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| **Acute toxicity (Rat oral LD50)** | >300 mg/kg or none to mild | 50 - 300 mg/kg or moderate | 5 - 50 mg/kg or moderate to severe | <5 mg/kg or severe | <5 mg/kg or extreme |
| **Skin or eye irritation** | mild to moderate | moderate to severe | severe | severe to corrosive | corrosive |
| **Therapeutic dose (mg/day)** | ≥100 | ≥10, <100 | ≥1, <10 | ≥0.1, <1 | <0.1 |
| **Severity of therapeutic effect** | severity of the therapeutic effect can push the above dose into a higher cell | | | | |
| **Target organ toxicity NOEL** | >10 mg/kg/d | 1-10 mg/kg/d | 0.1-1 mg/kg/d | 0.01-0.1 mg/kg/d | <0.01 mg/kg/d |
| **Target organ severity** | severity of the toxicity can push the above NOEL into a higher cell | | | | |
| **Repro/dev tox NOEL** | >30 mg/kg/d | 3-30 mg/kg/d | 0.3-3 mg/kg/d | 0.03-0.3 mg/kg/d | <0.03 mg/kg/d |
| **Repro/dev tox severity** | severity of the toxicity can push the above NOEL into a higher cell | | | | |
| **Cancer dose** | >30 mg/kg/d | 3-30 mg/kg/d | 0.3-3 mg/kg/d | 0.03-0.3 mg/kg/d | <0.03 mg/kg/d |
| **Carcinogenicity potential** | severity of the toxicity can push the above NOEL into a higher cell | | | | |
| **No dose established, but effects…** | none to minor | minor to moderate | moderate to serious | serious | critical |
| **Mutagenicity/Genotoxicity** | negative/equivocal | likely / limited or based on *in vitro* | positive WOE including *in vivo* | positive WOE including *in vivo* | positive WOE and potent |
| **Inhalation and/or dermal absorption** | minimal | moderate | moderate to significant | significant | significant |
| **Speed of onset** | immediate | immediate | immediate to delayed | immediate to delayed | immediate to delayed |
| **Need for medical intervention** | little to none | moderate (not life threatening) | high (potentially life threatening) | high (potentially life threatening) | high (potentially life threatening) |
| **Warning properties / odor** | good | fair | poor | none | none |
| **Other** | none | none | Default: materials of unknown toxicity | may affect sensitive subpopulations | may affect sensitive subpopulations |
| **OEL range (mcg/m$^3$)** | ≥100 | ≥10, <100 | ≥1, <10 | ≥0.1, <1 | <0.1 |

# Toxicity/Potency Categorisation of Chemicals (SafeBridge System)

- **Category 1: Low Toxicity**

  **OEL >0.5 mg/m$^3$ (aspirin, NSAIDs)**

- **Category 2: Intermediate Toxicity**

  **OEL 10 µg/m$^3$ - 0.5 mg/m$^3$**

  **(oxycodone, ACE inhibitors, statins, insulin)**

- **Category 3: Potent (default)**

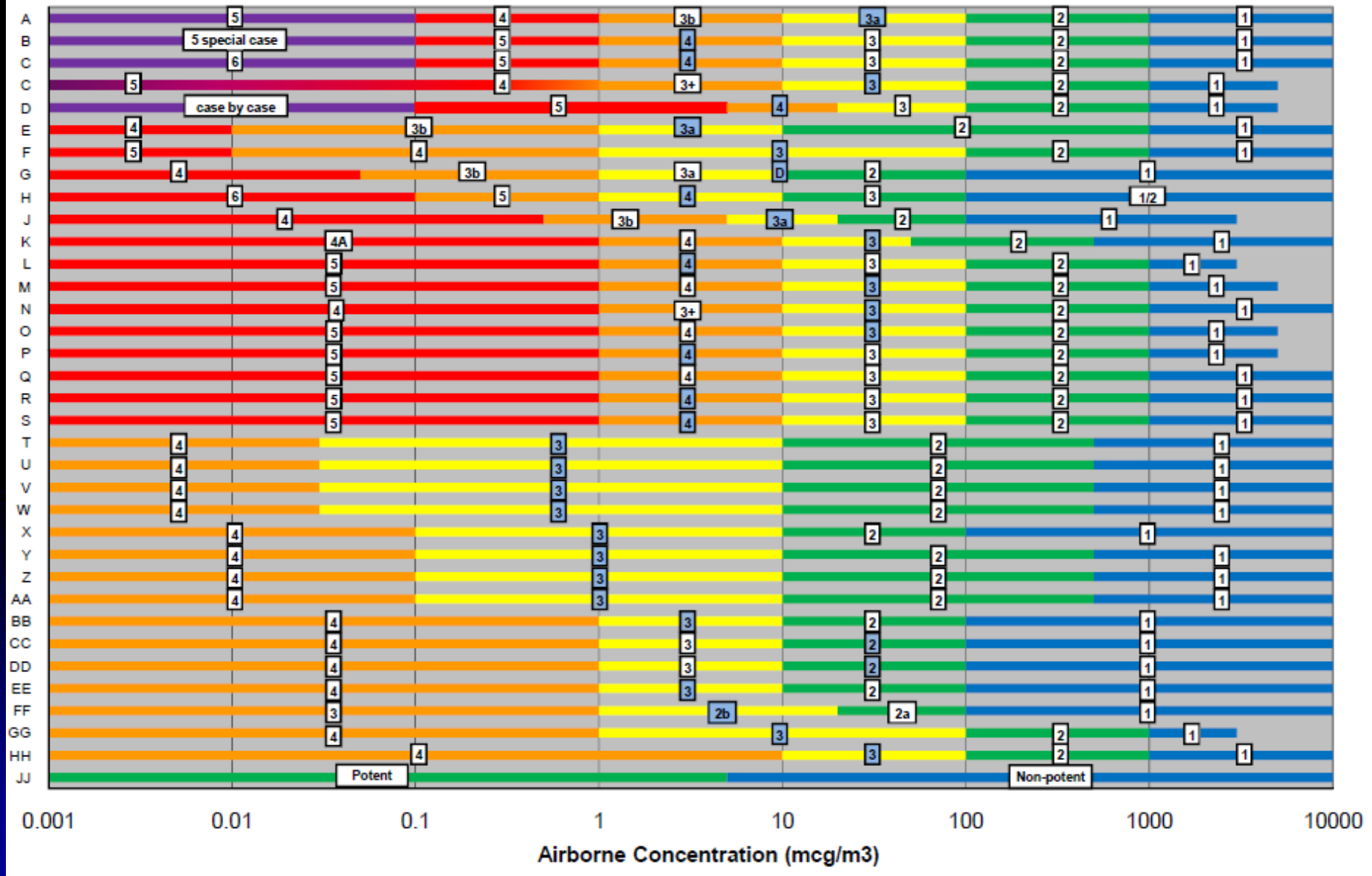
  **OEL 30 ng/m$^3$ - 10 µg/m$^3$**

  **(estradiol 17-β, ganciclovir, paclitaxel)**

- **Category 4: Highly potent**

  **OEL ≤ 30 ng/m$^3$ (nafarelin, leuprolide)**

# BANDING CUTOFFS 2008

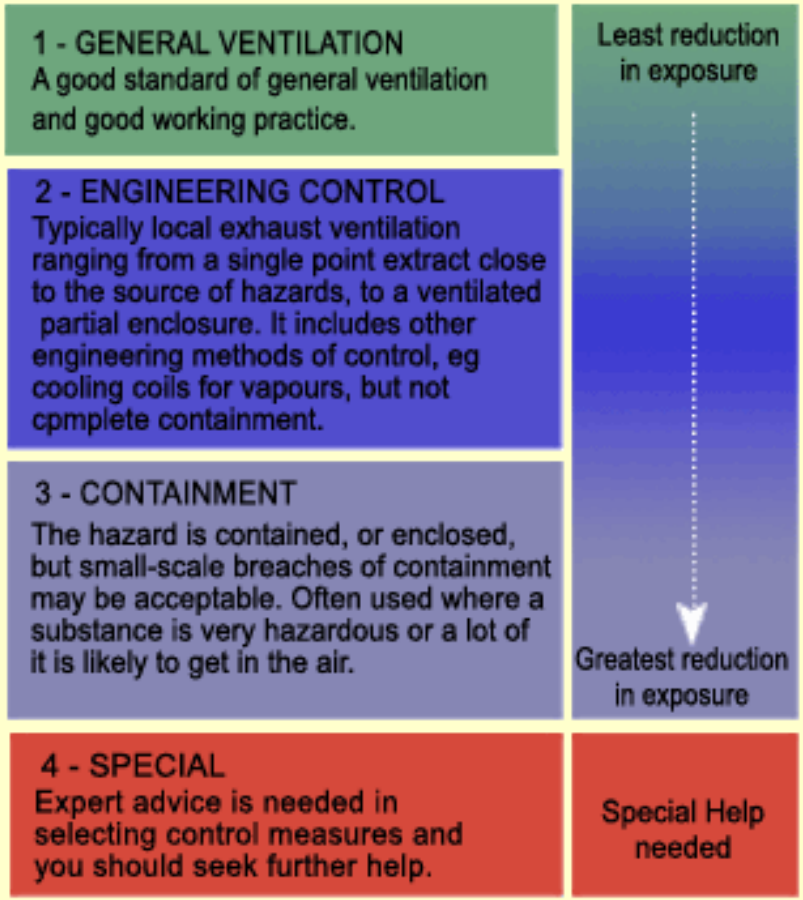


# Appropriate Control

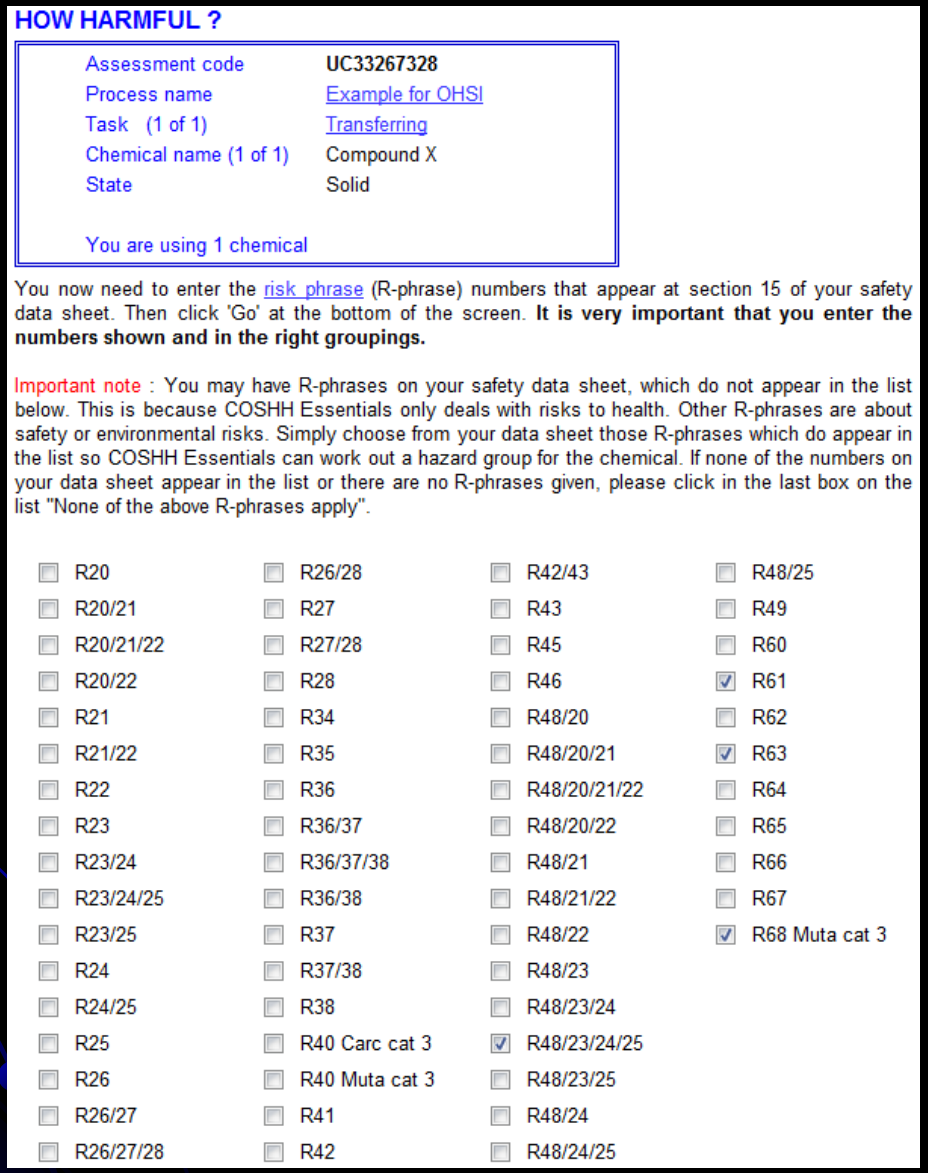
- Category or Band MUST be tied to Control
- What is “appropriate control”
- Control vs Containment
- How do you know the control or containment is effective?
- As systematic, scientific and defensible approach is needed

# COSHH Essentials

COSHH Essentials uses this information to select one of four control approaches:



# COSHH Essentials (2)



**HOW HARMFUL ?**

| | |
|---|---|
| Assessment code | UC33267328 |
| Process name | Example for OHSI |
| Task (1 of 1) | Transferring |
| Chemical name (1 of 1) | Compound X |
| State | Solid |
| You are using 1 chemical | |

You now need to enter the risk phrase (R-phrase) numbers that appear at section 15 of your safety data sheet. Then click 'Go' at the bottom of the screen. **It is very important that you enter the numbers shown and in the right groupings.**

Important note : You may have R-phrases on your safety data sheet, which do not appear in the list below. This is because COSHH Essentials only deals with risks to health. Other R-phrases are about safety or environmental risks. Simply choose from your data sheet those R-phrases which do appear in the list so COSHH Essentials can work out a hazard group for the chemical. If none of the numbers on your data sheet appear in the list or there are no R-phrases given, please click in the last box on the list "None of the above R-phrases apply".

| | | | |
|---|---|---|---|
| ☐ R20 | ☐ R26/28 | ☐ R42/43 | ☐ R48/25 |
| ☐ R20/21 | ☐ R27 | ☐ R43 | ☐ R49 |
| ☐ R20/21/22 | ☐ R27/28 | ☐ R45 | ☐ R60 |
| ☐ R20/22 | ☐ R28 | ☐ R46 | ☑ R61 |
| ☐ R21 | ☐ R34 | ☐ R48/20 | ☐ R62 |
| ☐ R21/22 | ☐ R35 | ☐ R48/20/21 | ☑ R63 |
| ☐ R22 | ☐ R36 | ☐ R48/20/21/22 | ☐ R64 |
| ☐ R23 | ☐ R36/37 | ☐ R48/20/22 | ☐ R65 |
| ☐ R23/24 | ☐ R36/37/38 | ☐ R48/21 | ☐ R66 |
| ☐ R23/24/25 | ☐ R36/38 | ☐ R48/21/22 | ☐ R67 |
| ☐ R23/25 | ☐ R37 | ☐ R48/22 | ☑ R68 Muta cat 3 |
| ☐ R24 | ☐ R37/38 | ☐ R48/23 | |
| ☐ R24/25 | ☐ R38 | ☐ R48/23/24 | |
| ☐ R25 | ☐ R40 Carc cat 3 | ☑ R48/23/24/25 | |
| ☐ R26 | ☐ R40 Muta cat 3 | ☐ R48/23/25 | |
| ☐ R26/27 | ☐ R41 | ☐ R48/24 | |
| ☐ R26/27/28 | ☐ R42 | ☐ R48/24/25 | |

# COSHH Essentials (3)

## HAZARD GROUP

| | |
|---|---|
| Assessment code | **UC33267328** |
| Process name | Example for OHSI |
| Task (1 of 1) | Transferring |
| Chemical name (1 of 1) | Compound X |
| State | Solid |
| R-phrase numbers | R48/23/24/25, R61, R63, R68 Muta cat 3 |
| Hazard group | E |

You are using 1 chemical

Please read this information and then click 'Go' at the bottom of the page.

The chemical **Compound X** belongs to the hazard group : **E**


The chemical **Compound X** may also cause harm if in contact with skin or eyes.

Warning : The chemical you are using has been given the high hazard group of **E**. Before carrying on you may want to consider using a less harmful chemical.

- Please speak to your supplier to see if there is another chemical you can use which will do the job satisfactorily.
- You may want to use the chemical in a less harmful form, eg use pellets instead of powder.
- You may also want to think about changing the process, for example using less of the chemical or a lower process temperature.

This will reduce the risk of ill health to your workers and make what you have to do, simpler and cheaper.

You can find more information in Seven steps to successful substitution of hazardous substances (This is on the subscription area of hsedirect).

In some circumstances **experts** with detailed information on the chemical can override the hazard grouping. **Click here to do this**.

# And then there was REACH and CLP

- Registration, Evaluation, Authorisation & restriction of CHemicals
- CLP – Classification, Labelling and Packaging
- Exposure Scenarios must be developed (when a material is manufactured in >10 tonnes/a)
- Must include risk management measures and operational conditions that ensure that the risks from uses of the substance are adequately controlled
- Need to be developed to cover all identified uses.
- To be used as a tool for communicating operational conditions of use and risk management conditions of use through the supply chain
- Will develop scope and coverage over time

# A Systematic Approach to Handling Potent Pharmaceutical Compounds

- Identify hazard potential of incoming via compound questionnaire, SDS, Literature review (GATEKEEP).
- Develop occupational health categorisation for early stage compounds
- Institute control/containment measures based on category/process/experience
- Develop written SOPs
- Train employees
- Develop OEL and air monitoring method to verify control measures and work practices

# Developing a Systematic Process to Handling Chemicals (continued)

- Verify process through:
  - Periodic assessment
  - Air monitoring and control implementation
  - Maintenance and testing of controls
- Health surveillance

# Control for Different Working Environments

- R&D Laboratories
- Kilo-Lab
- Pilot Plants
- Full Scale Production

# Laboratory Handling Practices
# Category 3

- Work Environment
  - A designated area for handling compounds
  - Work surfaces are to be cleaned daily; if absorbent paper is used it should be changed daily
  - No open handling of powders should be a priority; powder handling should be done in a powders weighing hood, a glove box or other approved ventilation system
  - Solutions can be handled outside a containment system or without local exhaust ventilation during procedures with no potential for aerosolisation
- PPE
  - Appropriate gloves, lab coat, safety glasses
  - Respirator selection appropriate to task

# Laboratory Handling Practices Category 4

- **Work Environment**
  - A designated area for handling compounds required
  - Work surfaces are to be cleaned daily; if absorbent paper is used it should be changed daily
  - No open handling of powders; work only to be done in isolators, gloveboxes or approved ventilated enclosures
  - Powder should be put into solution or tightly capped container for transfer
  - Local exhaust not required for solutions containing <100 mg if no potential for aerosolisation
- **PPE**
  - Appropriate gloves, lab coat, safety glasses
  - Air purifying respirators must be worn by all personnel in the immediate area if engineering controls are unavailable

# Production/Pilot Plant Handling Practices Category 3

- Work Environment
  - High degree of process containment, enclosure, local exhaust ventilation, and/or isolation/barrier technology
  - Negative/positive air and buffer zones required
  - Closed material transfer, no open handling
  - Production change areas
  - Controlled access
- PPE
  - Category 1 plus:
  - PAPR or air-supplied respirator with loose fitting facepiece
  - specifically selected chemical protective clothing

# Production/Pilot Plant Handling Practices Category 4

- **Work Environment**
  - Total process containment/isolation
  - Separated/dedicated work areas
  - Secured and restricted access
  - Highly specialised ventilation system
  - Failure protection
  - Clean in place; automation emphasis
- **PPE**
  - Category 3 for exposure situations

# Hierarchy of Control

- Elimination
- Substitution
- Engineering controls (“hardware”)
- Administrative controls (“software”)
- Personal Protective Equipment
  - PPE
  - RPE

# Engineering Controls (“Hardware”)

- Facility Design
  - Buildings and room layouts
  - HVAC (air pressure differentials)
- Control/Containment Equipment

# Administrative Controls “Software”

“Software” in this context is how you operate the “hardware”

**TECHNIQUE**

**PEOPLE**

**SOPs**

**TRAINING**

**MANAGEMENT SYSTEMS**

**CULTURE**

# Facility Design Considerations

- Smooth and logical flows
- Facility room air pressure relationships
- Access, ingress and egress arrangements
- Airlocks and ante-rooms
- HEPA filtered room air – one pass – no recirculation
- Delineate potent compound works areas and control accordingly
- Specify appropriate control devices

# Traditional Engineering Control Equipment Approaches

- Fume Cupboards
- Local Exhaust Ventilation (LEV)
- Directionalised laminar flow (booths)
- Other
  - enclosures of specific parts and containers
  - vacuum transfer

# Advanced Engineering Control Approaches ("Hardware")

- Process containment
  - barriers/isolators
  - bag techniques
- Closed processing and transfer systems
  - vertical process trains
  - intermediate bulk containers (IBCs)
    - specialized connectors and valves (SBVs)
- Ventilated enclosures
  - powders weighing hoods
  - enclosures for subdividing, filling, sizing

# Ventilated Balance Safety Enclosure®

# Isolators

## Weighing and Dispensing

## Product Charging

# Occupational Hygiene Testing

- Worker airborne exposure assessments versus OELs or other limits
- Equipment containment  performance testing versus control performance targets (could be controlling to a specific band)
- Surface monitoring to assess “tracking” away from sources

# Personal Protective Equipment

- **Respiratory Protection**
- **Skin protection**

# Medical Surveillance

- Another layer of protection
- Should target anticipated effects in the workforce
- Report and intervene early

# Limitations of Banding Systems

- Does not replace limit setting and air monitoring
- Does not demonstrate a health protective environment
- Placement of early stage compounds is based on characteristics not exposure limits
- Compounds need to be re-evaluated as new data become available
- Requires experienced toxicologists and occupational hygienists to get it right
- Not adequate by itself to satisfy regulators for Big Pharma and Big Chem in UK and Eire

# Summary

- Understand the risks - toxicological, process and other
- Use “banding” systems intelligently to deal with early stage materials or to direct you to a control strategy- they are not “magic cookbooks”!
- Design and build well
- Specify equipment that is fit for purpose
- Verify for yourself that it works
- Use skilled and experienced staff
- Measure the effectiveness of your controls and “verify” that your banding system actually delivers
- Apply a systematic, science-based approach to safety