

Session C1. Regional, State, and Local Initiatives
Auditorium, C-111

FENTANYL TOXICITY, EXPOSURE AND RISK

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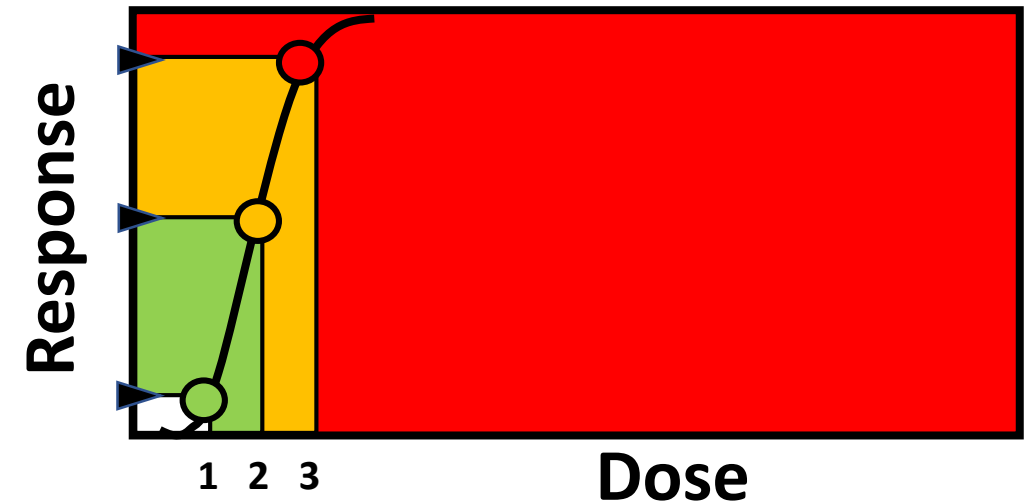
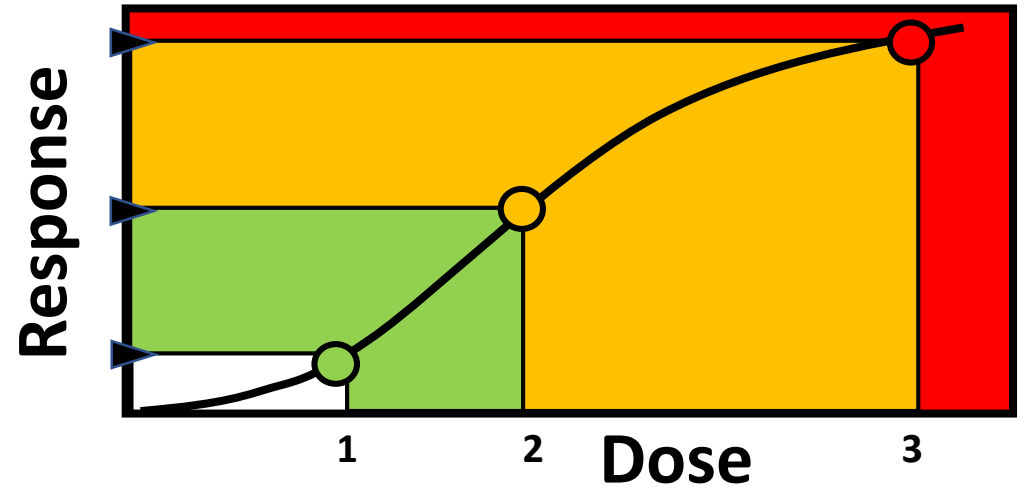
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TOXICITY: DOSE AND RESPONSE

“All things are poison and nothing is without poison; only the dose makes that a thing is no poison.”

- Paracelsus, 1536



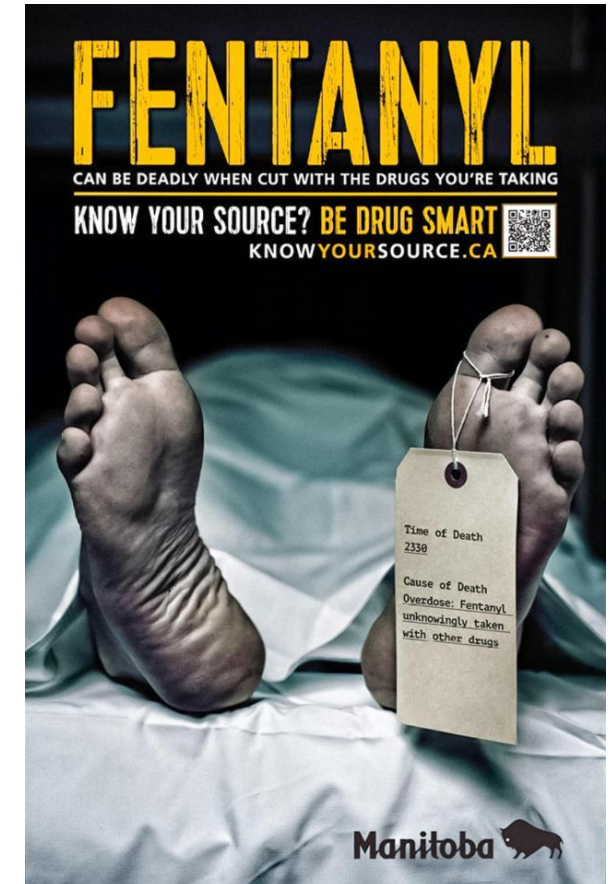
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FENTANYL EXPOSURE

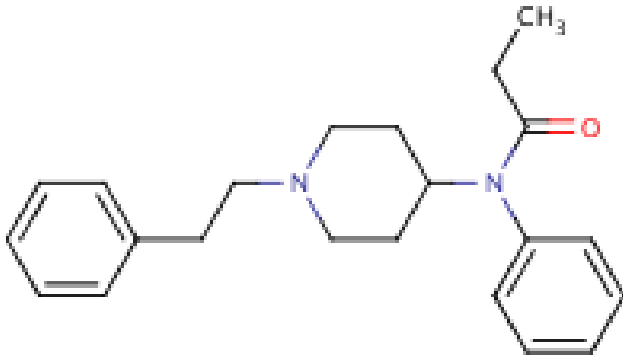
Marion County, Indiana

- Fentanyl-laced heroin causes in-home overdose
- Mother cleans house, dies from fentanyl exposure
- County Health Department refuses to direct clean-up, citing lack of guidance
- Marion County solicited the State of Indiana and Region 5 for guidance
- Region 5 is seeking **risk values as basis for clean-up goals**



Taken from the Sun UK
(Canadian Public Health Poster)

FENTANYL AND ANALOGS



Fentanyl



Carfentanil

Opioids; receptor-mediated effects
CNS depression, respiratory depression, death
Rapid onset of toxicity
Effective orally and by inhalation. Dermal?

**TARGET TISSUE DOSE ★
DRIVES THE RESPONSE**

Environmental Amount → Fentanyl in air

Human Exposure → Air inhaled

External Dose → Fentanyl inhaled

EXPOSURE

Internal Dose → Fentanyl absorbed into blood

Fentanyl absorbed by brain → Target Tissue Dose ★

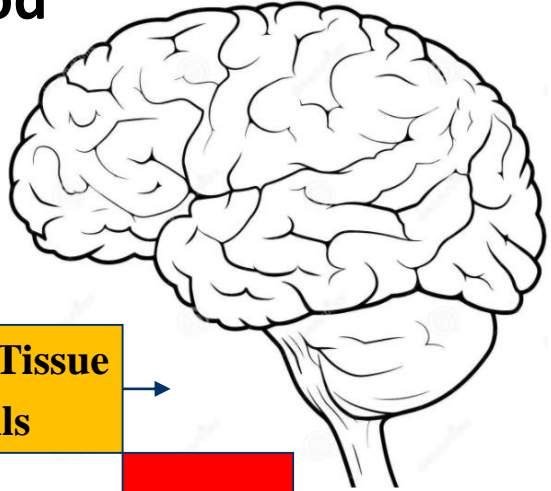
Fentanyl binds opioid receptor

Target Tissue Responds

Activated receptor causes toxicity

Target Tissue Fails

Death

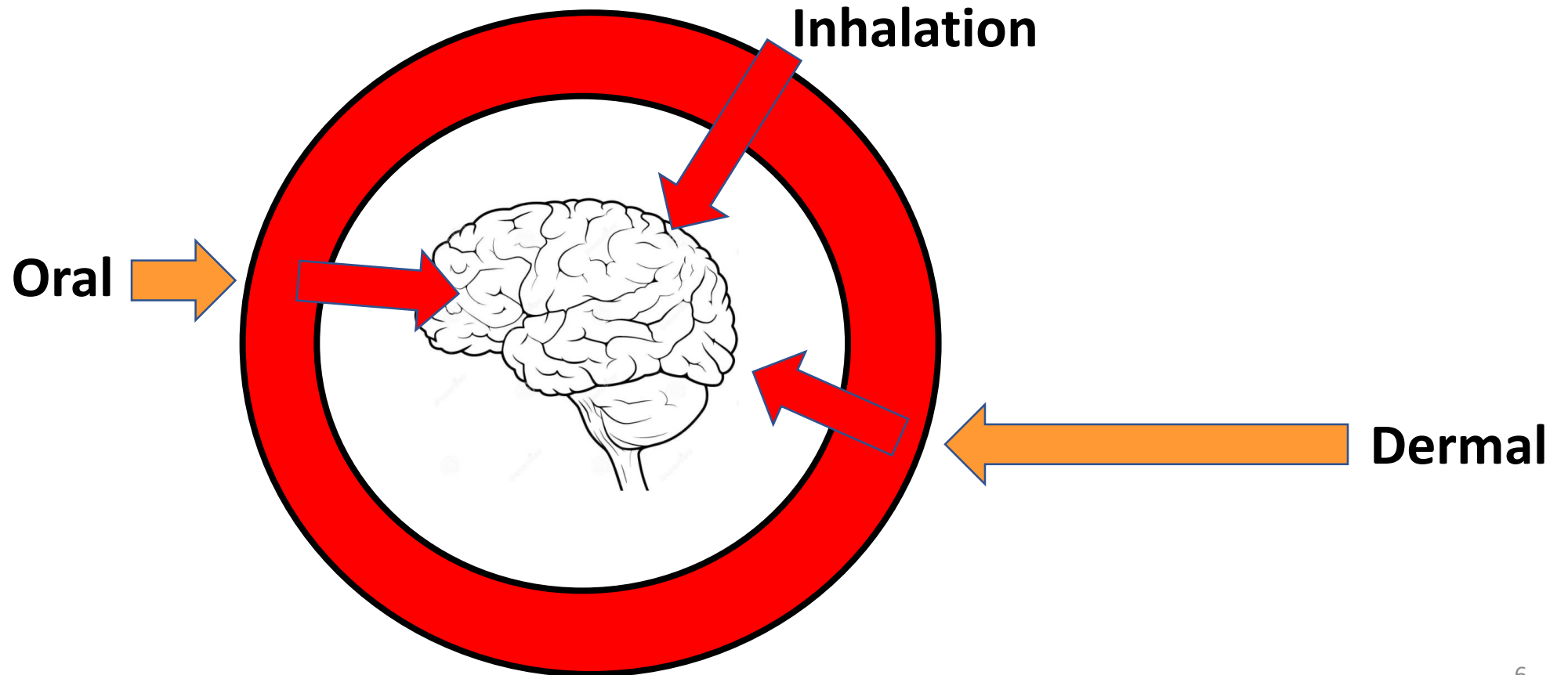


DOSE

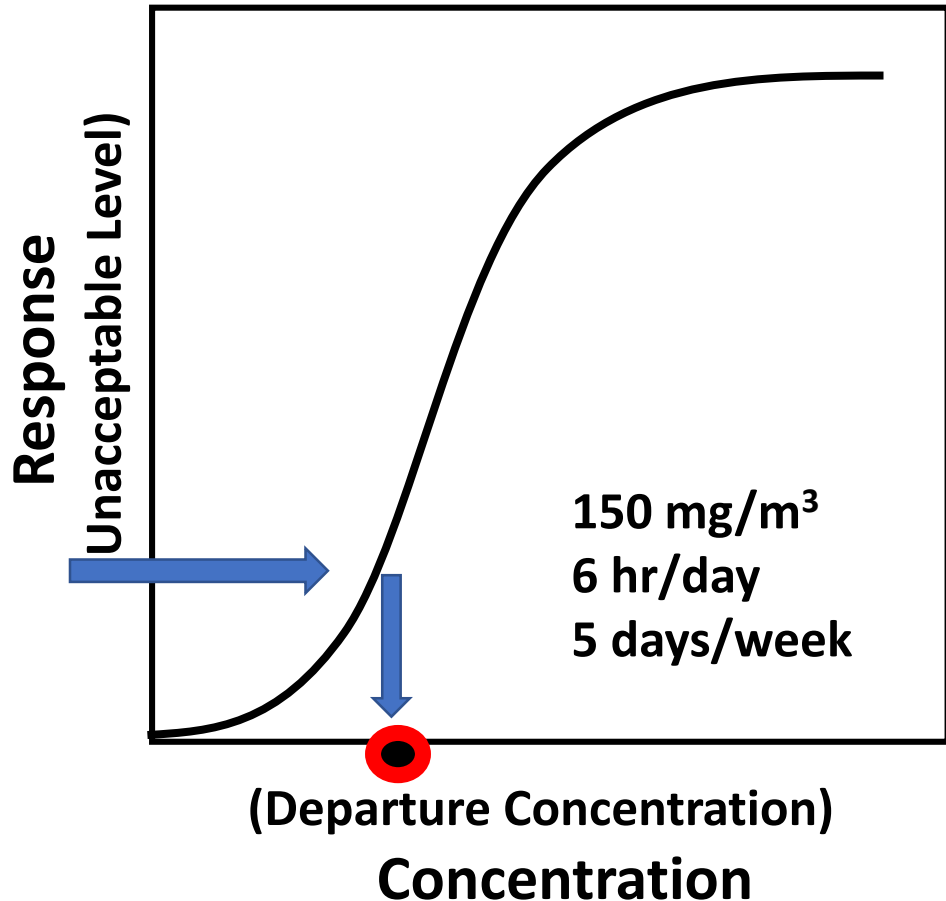
RESPONSE

FENTANYL BRAIN DOSE

Brain is **the** target organ, blood is the route of exposure
Route-specific biological barriers



Toxicity Data



Human Equivalent Concentration

Default: no tissue connection
Duration-adjusted concentration
Respiratory volume adjustment, or
Blood partitioning adjustment

Data-based: Toxicokinetics
Target tissue concentration

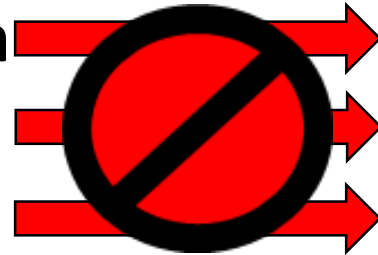
Human Equivalent Concentration

Default: no tissue connection

Duration-adjusted concentration

Respiratory volume adjustment,

Blood partitioning adjustment



Brain conc. not averaged

Not a respiratory tract toxicant

Not a gas or vapor

Data-based: Toxicokinetics

Target tissue concentration

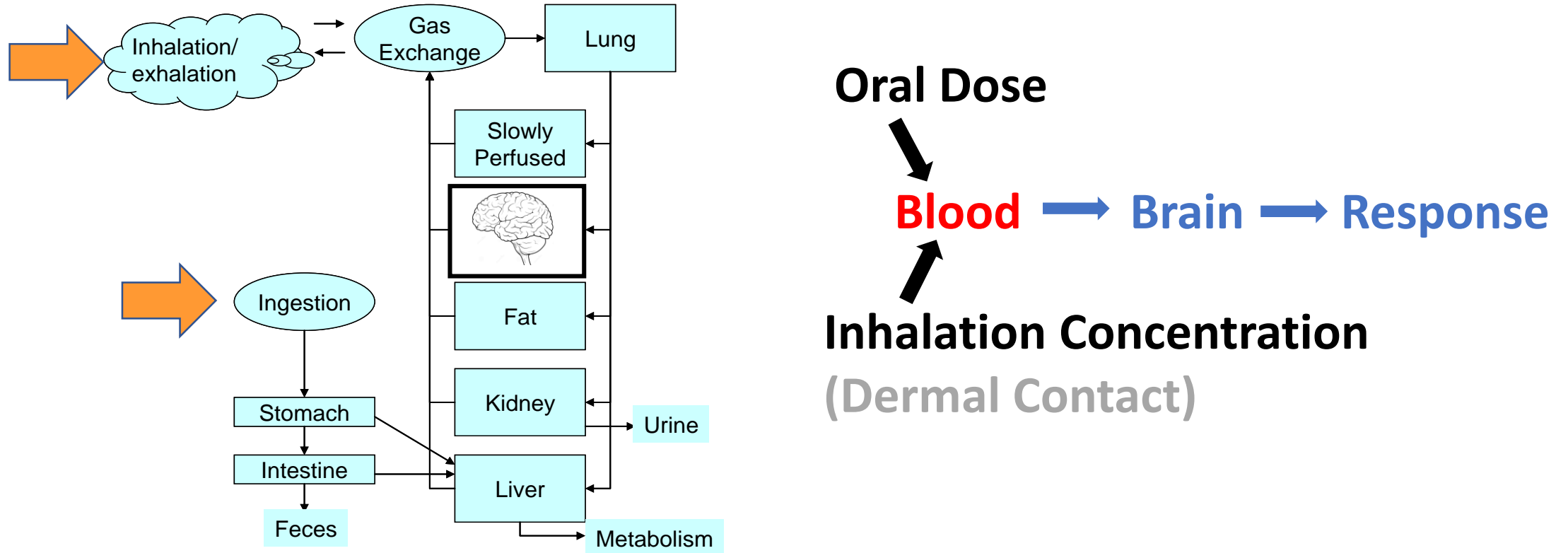


Uses toxicokinetic model

to estimate tissue concentrations

What methods are needed?

PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING



NHSRC's Peer Reviewed Fentanyl PBPK Model:
Shankaran et al. Toxicology and Applied Pharmacology, 273:464, 2013.

PBPK MODELING OF DOSES

Extrapolation of toxic tissue concentrations

- **Among species**
- **Within human population groups**
- **Between routes**
- **Over durations**
- **Over dose ranges**

PBPK model translates toxic doses to toxic tissue concentrations

PBPK models for EPA Assessments of: vinyl chloride, EGBE, benzene, ethylbenzene, formaldehyde, xylene, toluene, MEK, trichloroethylene, trichloroethane, methanol, carbon tetrachloride, dichloromethane, 1,4-dioxane, trimethylbenzene ...

Risk Assessment

$$\frac{\text{Human Dose}}{\text{Uncertainty Factors}} = \text{Risk Value (e.g., RfD)}$$

Exposure Guidelines

$$\text{Guideline Value} = \text{Risk Value} \times \text{Environmental Media Exposure}$$

Clean-Up Goal

$$\text{Clean-Up Goal} = \text{Guideline Value} \times \text{Specific Considerations}$$

TOXICITY

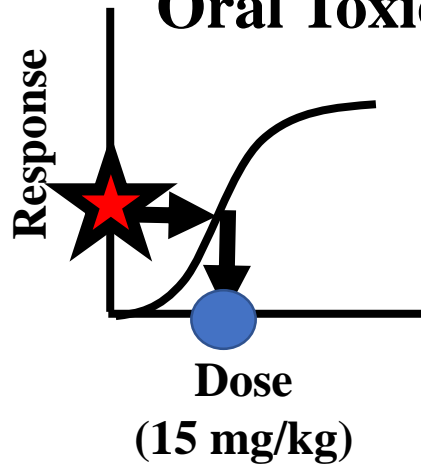
DOSE EXTRAPOLATION

RISK

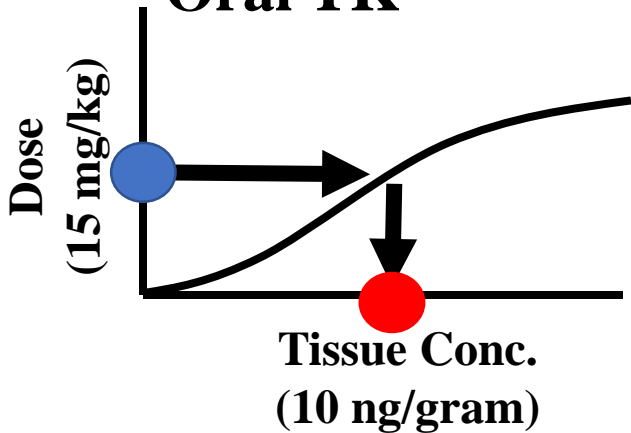
TOXICOKINETICS

Animal

Oral Toxicity

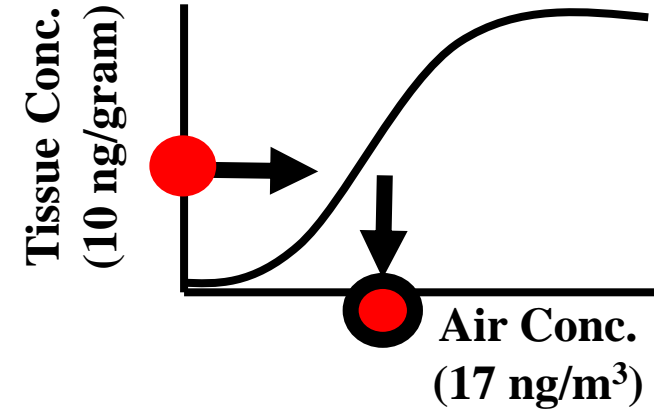


Oral TK



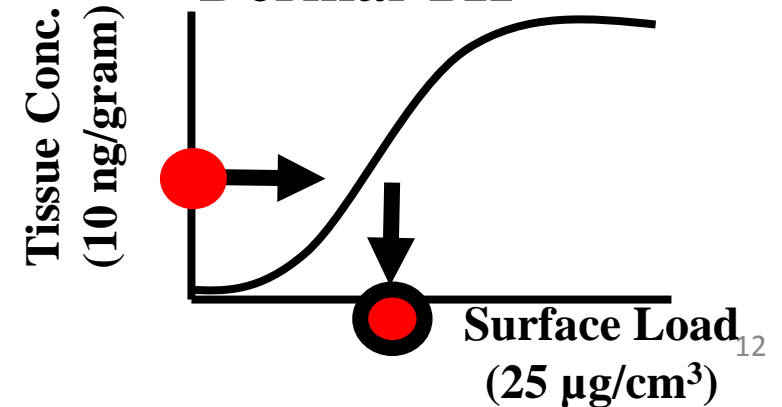
Human

Inhalation TK

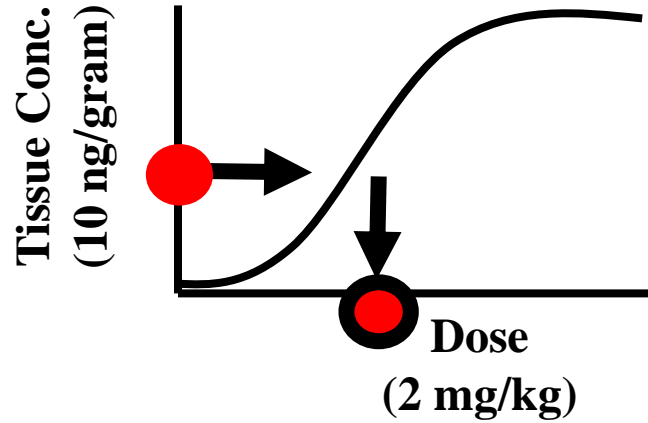


Human

Dermal TK



**Human
Oral TK**



INFORMING DEVELOPMENT OF A CLEAN-UP GOAL

- Complete the existing EPA draft risk values for Fentanyl
- Update toxicity, toxicokinetic information
- Extend peer reviewed PBPK model to dermal route
- Compute dermal toxic doses
- Characterize dermal exposure effects
- Determine toxic dermal contact characteristics

- Ensure analytical detection capacity
- Ensure effective decontamination procedures

