1,4 Dioxane:
What You Should Know

Robert K. McLellan, MD, MPH, FACOEM
Chief, Occupational and Environmental Medicine
Dartmouth-Hitchcock

Professor of Medicine,
Community and Family Medicine,
And The Dartmouth Institute
Geisel School of Medicine

Dartmouth-Hitchcock

What I Will Do Today

- Explain basic principles of how chemicals can cause harm to humans
- Discuss how 1,4 Dioxane could affect you or your children's health
- Examine the idea of "risk" of future health problems
- Discuss the idea of a community health study
- Outline some steps you can take to understand and manage your risks
- Listen to and address your questions
- Additional health resources for you and your physician

Today, I will not …

- Have answers to all of your questions,
  - But we will capture them so that we can get answers to you if answers do exist
  - Or refer questions outside my role or expertise to the appropriate resource
  - In some cases, there simply are not answers
- Provide personal medical advice

Dartmouth-Hitchcock

Whether any chemical causes harm, depends on….

- Its toxicity and/or cancer potency
- Its chemical and physical properties
- Your dose
- Your individual susceptibility

How do we learn about the health effects of chemicals?

- Epidemiology
- Animal toxicology
- In vitro (lab) experiments on human/animal cells and genes
- Similarity to other chemicals

Dartmouth-Hitchcock

1, 4 Dioxane Human Data

	Death	Systemic: Acute	Systemic: Intermediate	Systemic: Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●		●						●
Oral										
Dermal	●	●								

ATSDR 2012

1, 4 Dioxane Animal Data

		Systemic								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●		●				●
Oral	●	●	●	●		●		●	●	●
Dermal	●	●	●							●

ATSDR 2012

Chemicals Differ in Toxicity: Capacity to Cause Harm at a Specific Dose

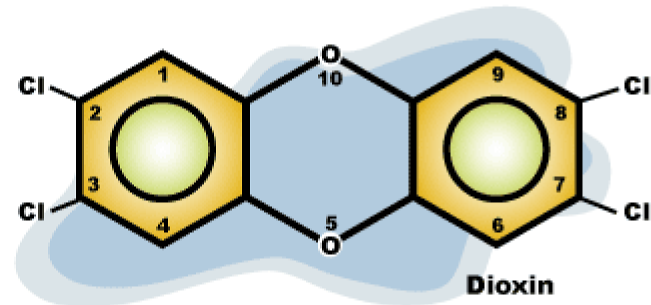
Low toxicity

High toxicity

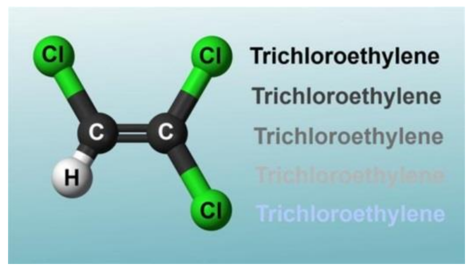
Chemicals Differ in Capacity to Cause Cancer

- Weight of evidence
  - Degree of certainty that it does cause human cancer
- Potency
  - Dose to increase risk of cancer by a certain amount

Chemical Carcinogens Differ in Potency:



0.000000033 ug/m^3



0.25 ug/kg/d

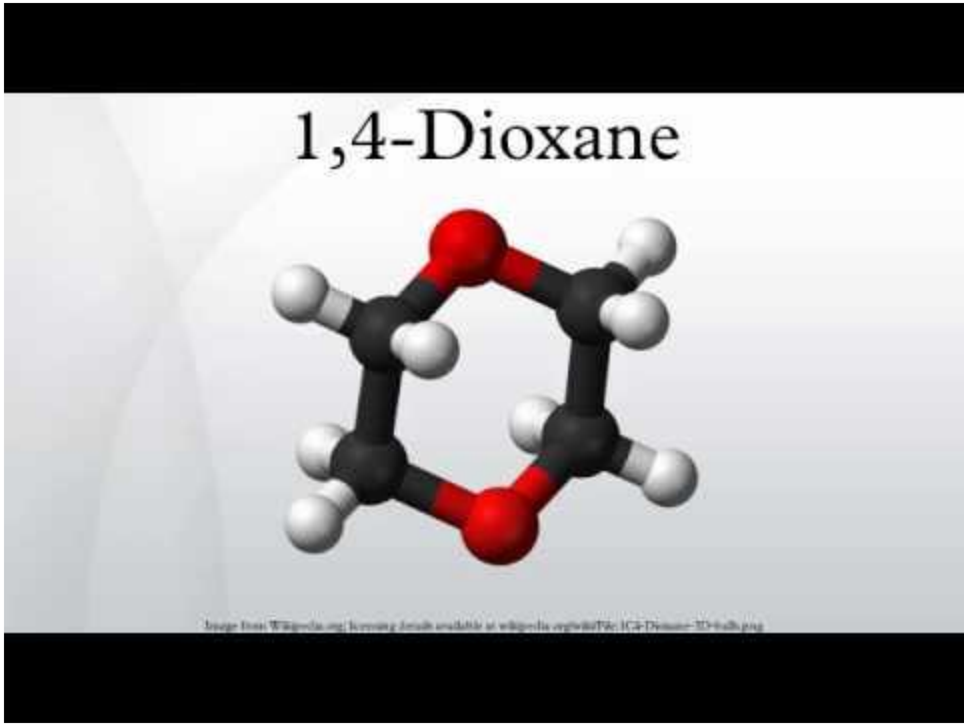
100 ug/kg/d

Potency as reflected by
Oral Slope Factors

Dartmouth-Hitchcock

1, 4 Dioxane *Can* Cause Harm

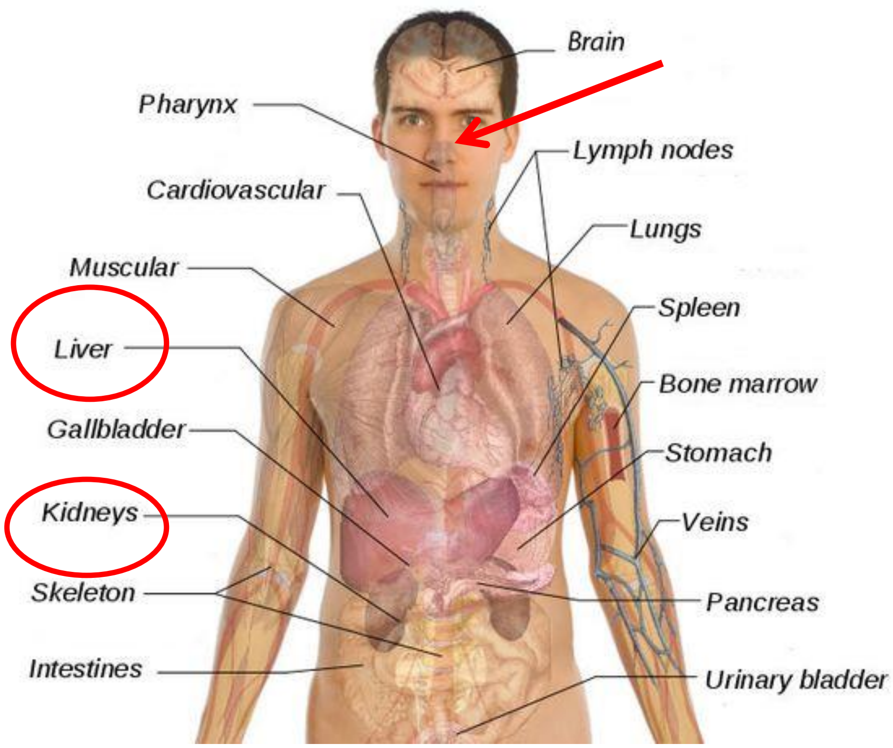
- Definite toxic effects
  - Death
  - Organ damage
  - Safety thresholds
- Likely carcinogenic effects
  - Probably increases risk of certain cancers
  - Assume no threshold
- Unknown/unclear reproductive and developmental effects
  - Safety thresholds



Dartmouth-Hitchcock

Very High Dose Exposures: Acute Toxic Effects

- Human evidence
  - Occupational
  - Inhalation very high levels
- Death
- Critical organ dysfunction (temporary) or damage
  - Liver
  - Kidney
  - Nose and Respiratory irritation



Dartmouth-Hitchcock

Long Term Lower Dose Exposures: Chronic Toxic Effects

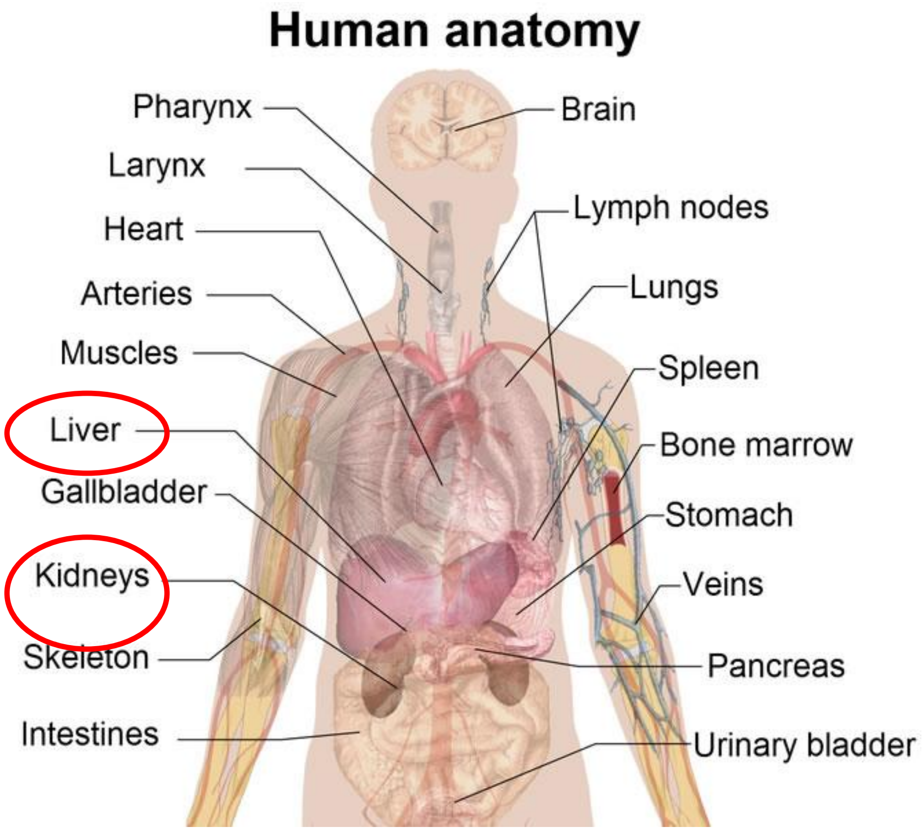
- Very Limited Human evidence
- Animals
  - Organ damage
    - Liver
    - Kidney
    - Nose

Potential Reproductive and Developmental Effects?

- Very limited and uninterpretable human evidence
  - Mixed solvent exposure of workers
- Limited animal data
  - Inhalation
    - No effects
  - Oral
    - No conclusive evidence
    - Very high levels in rats produced lower wt offspring and minor bone problems

Potential Cancer Effects

- Human evidence
  - Very limited
  - No evidence that it causes cancer
- Animal evidence
  - Definite animal carcinogen
    - Liver
    - Kidney
    - Nose
- Likely human carcinogen



The dose makes the poison.

Paracelsus (1493-1541)

Dose:
Concentration, Exposure And Duration

Safe Dose

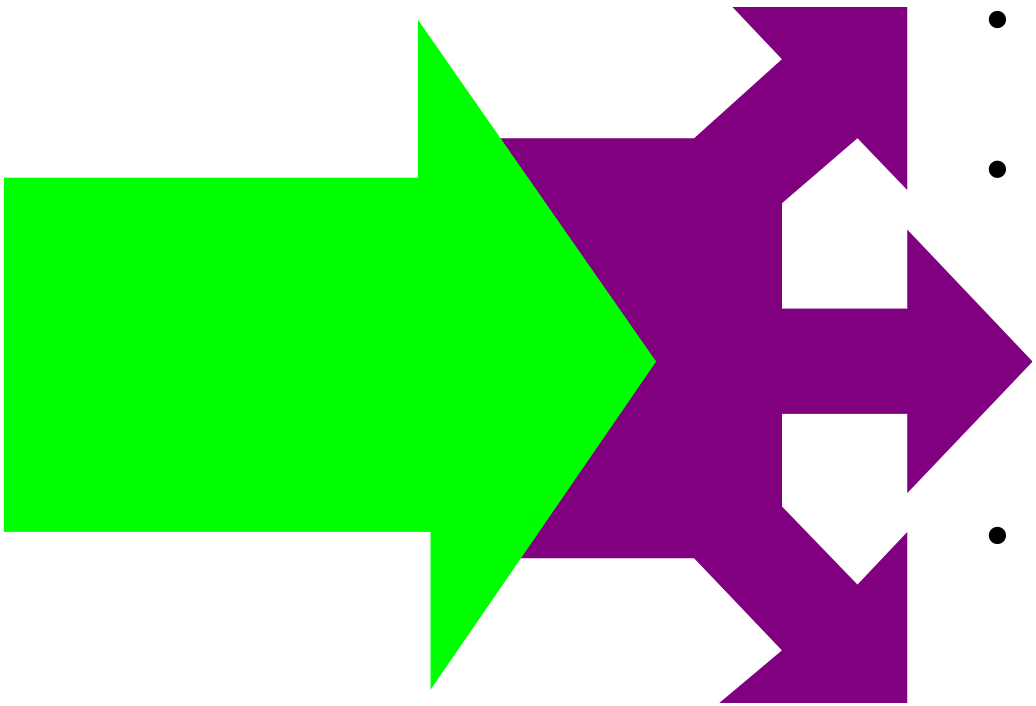
No Exposure,
No Dose
No harm

Dangerous Dose

Water Concentration: Amount in the Water

- 1,4 Dioxane concentration measured in ug/L
- Microgram (ug)
  - 1 millionth of a gram
- ug/L
  - Micrograms per liter of water or parts per billion (ppb)
  - 60 billion drops in an olympic pool
- Levels detected in 2 drinking water wells
  - ~ 6.0 ug/liter or 6 ppb
  - ~ 0.3 ug/liter or 0.3 ppb

Chemical and Physical Properties



- How the substance gets into the body (Absorption)
- Where it goes in the body (Distribution and Storage)
- How it is processed (metabolism)
- How it leaves the body (Excretion)

Routes of Exposure

Host

Agent

80% absorption

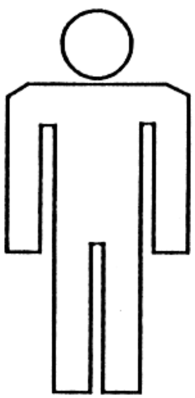
Inhale

1% absorption

Skin Contact

Ingest

100% absorption

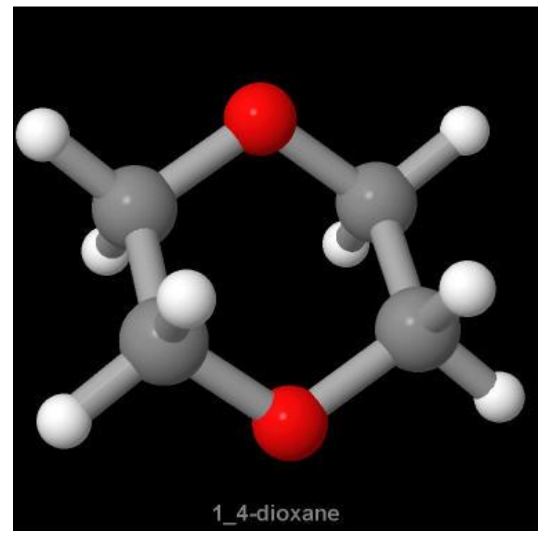


Air

Water

Soil

Food



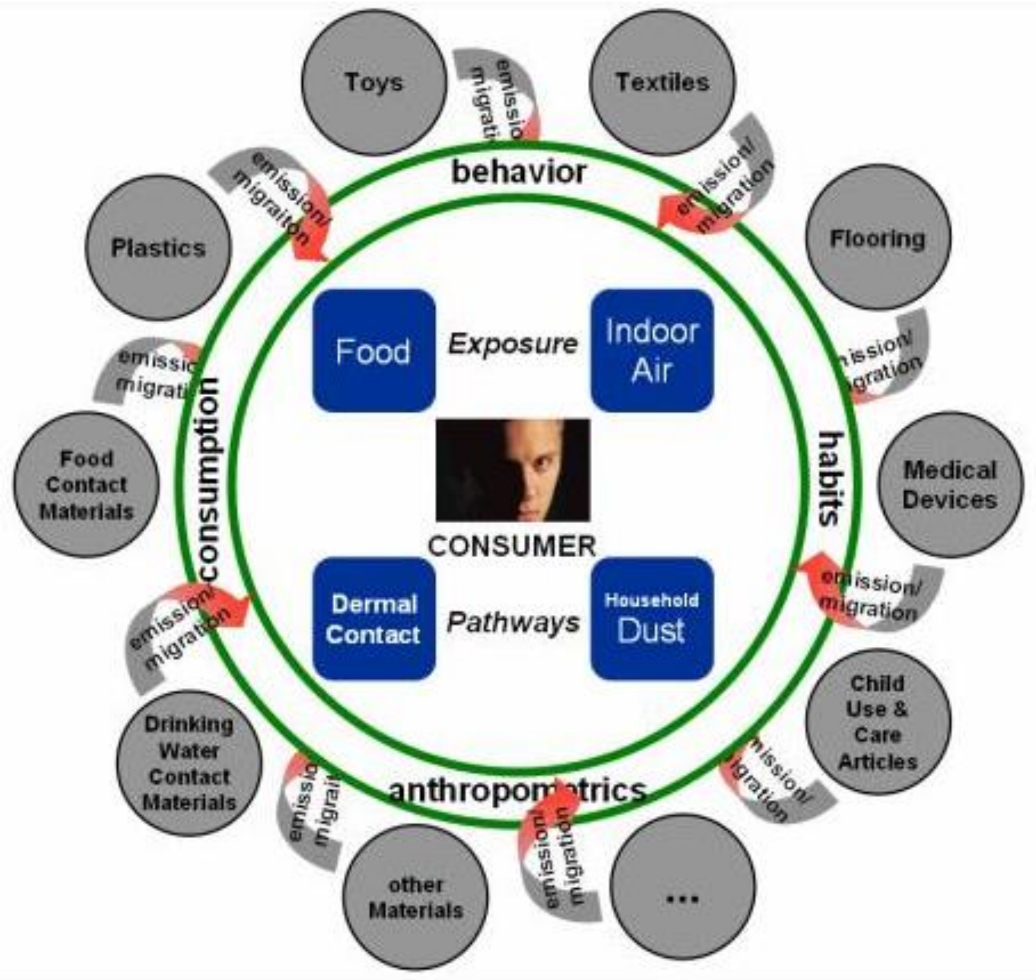
Other: transplacental (uncertain), lactation (possible for high dose)

Testing for 1,4 Dioxane in the Body

- 1,4 Dioxane or by-product (HEAA metabolite) *can* be measured in urine of highly exposed workers suffering toxic effects
- BUT
  - 1,4 Dioxane excreted (disappears) within a day of exposure
  - Not present in the environment at levels sufficient to be detectable in urine

Total Exposure Matters

- Sources of 1,4 Dioxane
  - Rennie Farm waste site
  - Consumer products
- Hundreds of other chemical contaminants in our environment
  - Low levels of many of these in all of us, even in animals at the earth's poles



Other Sources of Environmental Exposure to 1,4 Dioxane

- Personal care and household products
  - Shampoos/Conditioners
  - Bubble bath
  - Sunscreen
  - Cosmetics
  - Detergents
- Look for
  - Sodium lauryl sulfate
  - PEG compounds (for example, PEG-150, PEG 6 methyl ether, etc.)
- Food containers/wrapping
- Pharmaceuticals
- Adhesives, paint strippers, grease, etc
- Plastics like PVC

Formaldehyde & 1,4 Dioxane

You will never see 1,4 Dioxane listed on the ingredients label. It is not mandated by the government because it is a byproduct from processing cheap harsh chemicals.

This is only a sample of the products listed on the "Household Products Database" containing Formaldehyde or 1,4 Dioxane

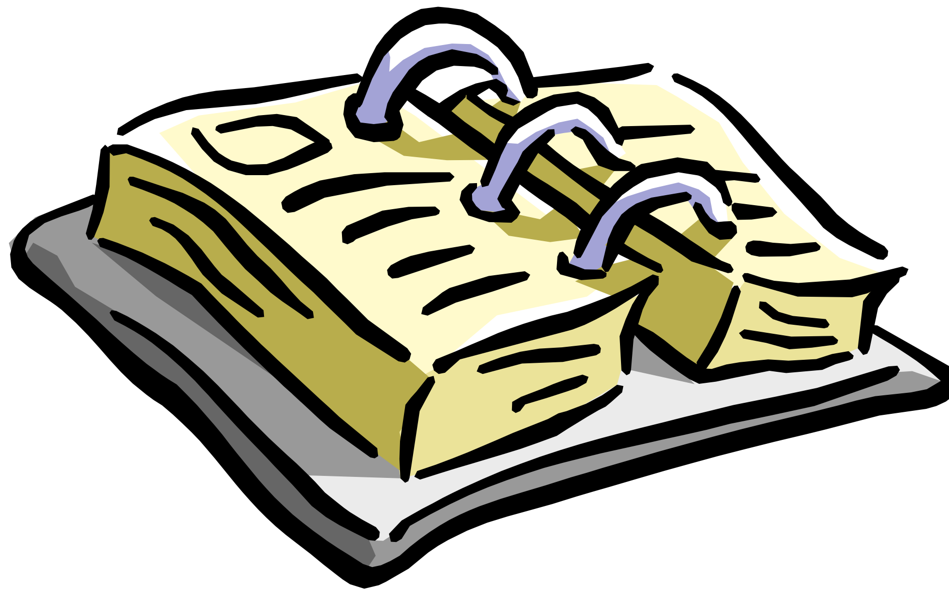
https://householdproducts.nlm.nih.gov/

Dartmouth-Hitchcock

Dose Depends on Concentration and Duration of Exposure

- Short term (acute)

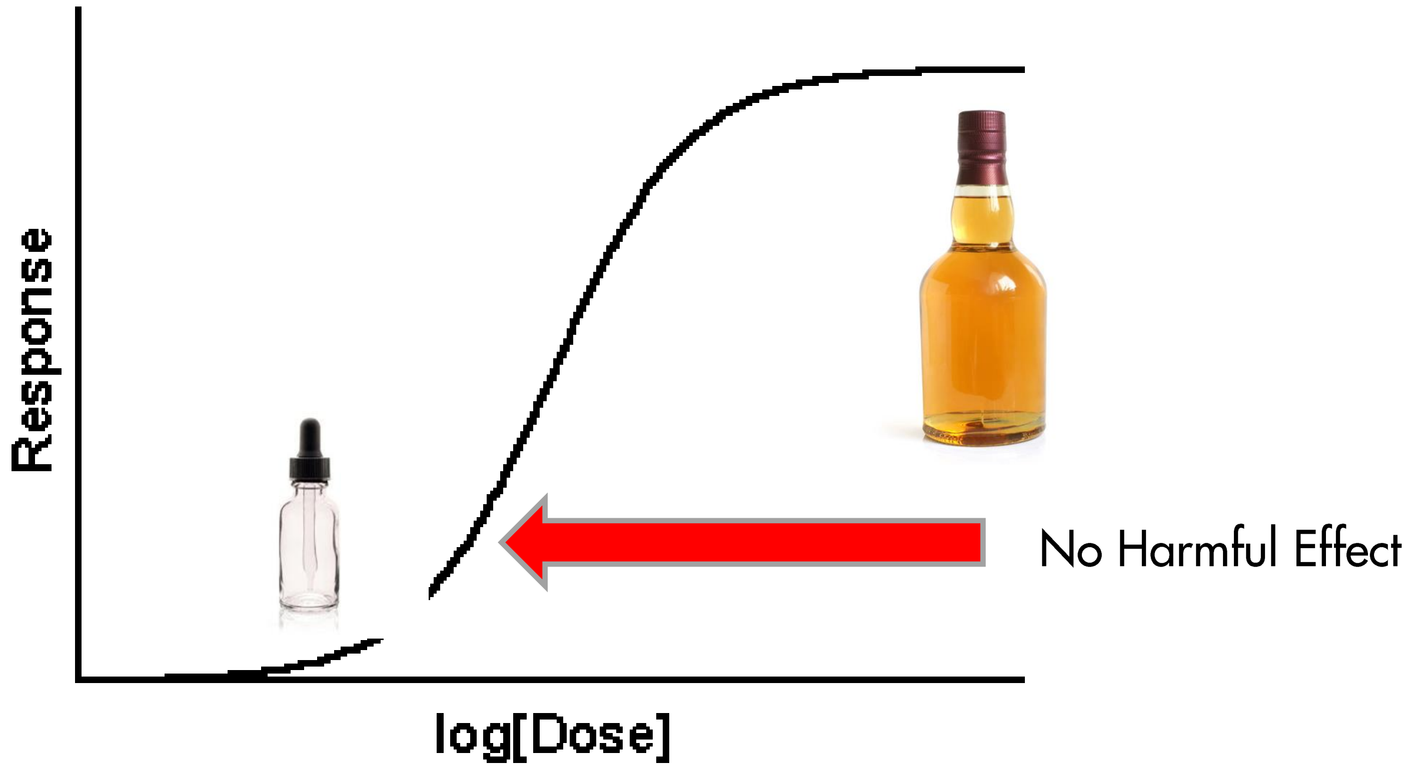
- Long term (chronic)



Dose - Response

- Response of the body to a chemical is directly dependent on the dose:
  - Concentration, exposure (route), and duration
- *All* chemicals are toxic at sufficient dose
- Most chemicals are not toxic below a safety threshold
- We usually assume that carcinogens have no thresholds, but the dose matters: lower dose, lower risk

Dose Response and Safe Threshold



Dartmouth-Hitchcock

Individual Susceptibility

- Demographic factors
  - Age
  - Gender
- Lifestyle factors
- Genetic makeup
- Health problems

Dartmouth-Hitchcock

Likelihood (Risk) of Harm Depends on Toxicity + Exposure + Susceptibility

- Harm can only occur when *exposure* to a toxic substance occurs
- The likelihood of harm (risk) increases as
  - The harmfulness (toxicity/carcinogenicity) of the substance increases
  - The dose increases
    - *Dose = concentration* (amount) and *duration* of exposure
  - Susceptibility increases

Dose-Response: At What Dose May Harm Occur?

- Environmental safety threshold levels
  - *Protective of harm to the most susceptible individuals including children and fetuses*
  - *Protection increased by setting levels well below those observed to cause harm*
- ATSDR sets Minimum Risk Levels (MRLs) as safety thresholds for non-cancer effects based on best evidence of most sensitive effect for specific exposure duration.
  - If human evidence not available, adjust for uncertainty about possible difference between animals and people and different susceptibility of people

Oral MRL for 1,4 Dioxane

- Oral MRL for chronic long term exposure (more than 365 days)
    - 100 ug/kg/day
        - Based on liver damage in rats
        - 100 times lower than rat harmful dose
    - Minimal risk of harm by ingesting 2 liters/day
        - Avg adult man (70kg) = 3500 ug/liter of water
- Oral MRL for acute exposure (less than 14 days)
    - 5000 ug/kg/day
        - 100 times lower than rodent harmful dose

Inhalation MRL for 1,4 Dioxane

- Inhalation MRLs for chronic exposure
  - 0.03 parts per million (ppm) in air
  - Based on nasal lesions in rats
  - 300 times lower than harmful rat dose
- Inhalation MRL for short term exposure (acute)
  - 2 ppm in air
  - Based on no irritation in humans at 20 ppm
  - Set 10 times lower for human variability

Other Environmental Safety Thresholds

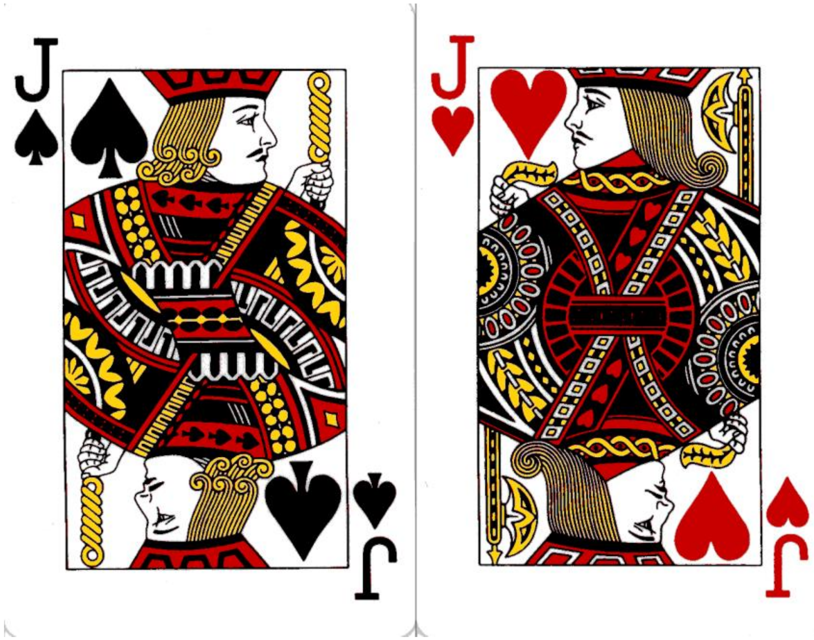
- EPA IRIS – protective of most susceptible for lifetime of exposure
  - Oral Reference Dose (RfD)
    - 30 ug/Kg/d
    - Based on rat liver/kidney toxicity
  - Inhalation Reference Concentration (RfC)
    - 30 ug/M^3

Likelihood of toxicity (Non-Cancer Effects) from environmental exposures at Rennie Farm extremely low based on current science and measured levels of contamination.

What about cancer risk?
If I am exposed to a carcinogen, won't I get cancer?

Risk = What are the chances?

- One eyed Jack (2/52)



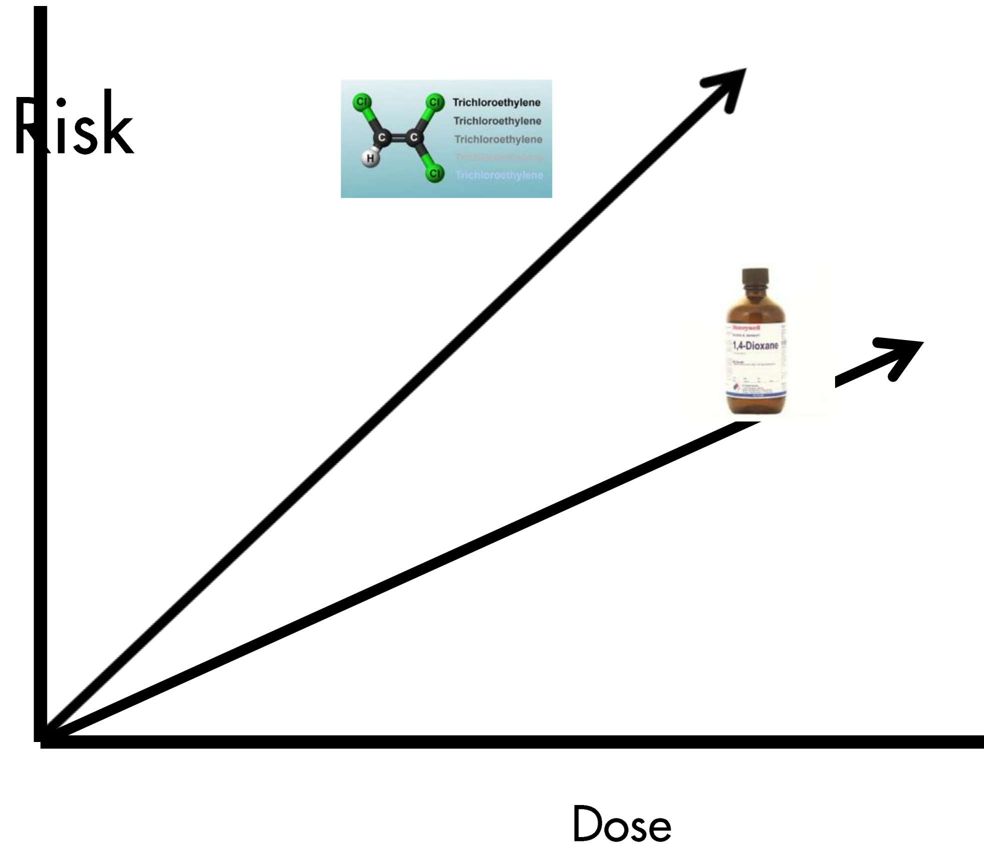
- A heart (1/4)

Extra Chance (Extra Risk):
add another one eyed Jack to the deck

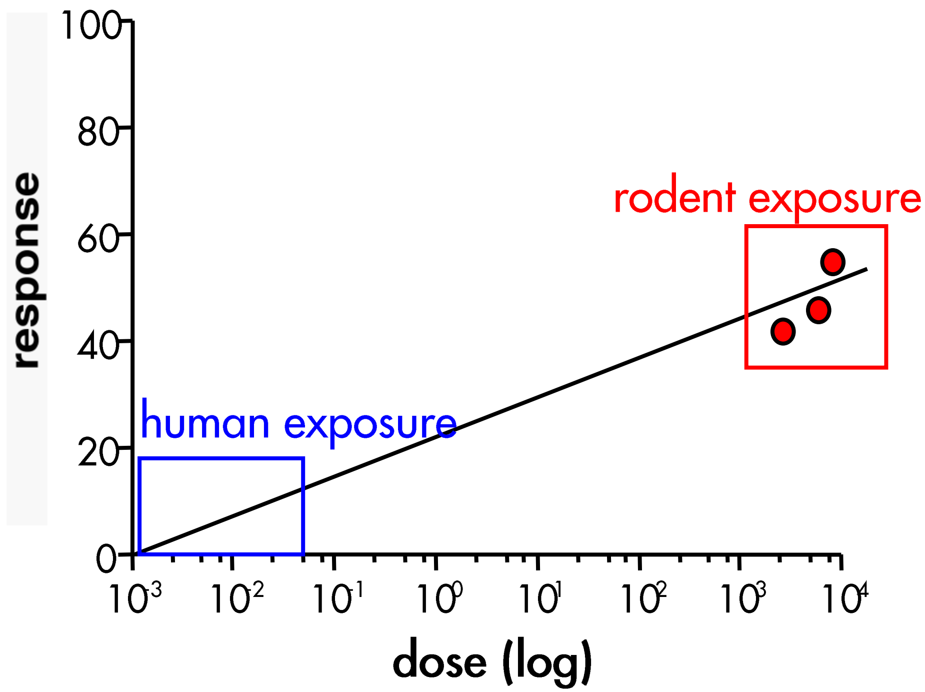
If you added 1, one eyed jack to a million decks of cards, you would have one more chance (excess risk) of pulling a jack

Cancer Risk

- Assume *any* dose increases risk
- Higher dose = higher risk
- Cancer potency
    - Steeper incline (slope) = higher risk



Estimating Cancer Risk from from rodent experiments (extrapolation)



Dartmouth-Hitchcock

EPA Cancer Risk Estimates*

Water Concentration	Risk Level
35 ug/L	1 excess cancer in 10,000
3.5 ug/L	1 excess cancer in 100,000
0.35 ug/L	1 excess cancer in 1,000,000

- 70 kg man drinking 2 liters of water for 70 years
- Based on studies of liver cancer in mice

Dartmouth-Hitchcock

Exposure to 1,4 Dioxane While Showering

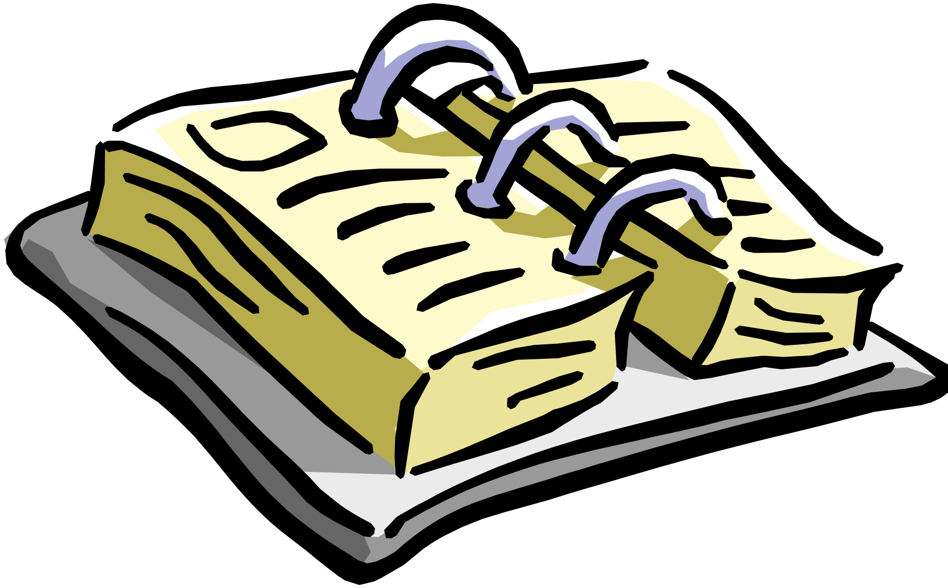
- Assume
  - Daily shower 33-45 mins
  - Closed bathroom 60 mins
- 24 ug/L for 30 yrs
  - 1/million excess cancer
- Total cancer risk of contaminated water
  - 97% drinking
  - 3% showering

Dartmouth-Hitchcock

Timing of Harmful Effect

- Soon (Acute)
  - High dose

- Delayed (Latent)
  - Lower dose



What is *your* risk of illness related to 1,4 dioxane?

- No exposure, no risk
- Based on detected levels negligible or no risk of toxic organ damage or dysfunction
- What about children
    - Uncertain whether more or less susceptible
    - BUT MRLs are very conservative and meant to protective most sensitive people in community
- What about breast feeding
    - Little transmission of 1,4 dioxane
- What about risk of reproductive, developmental effects?
    - Inadequate evidence

Treatment for 1, 4 Dioxane Exposure

- Remove from exposure
- No antidote

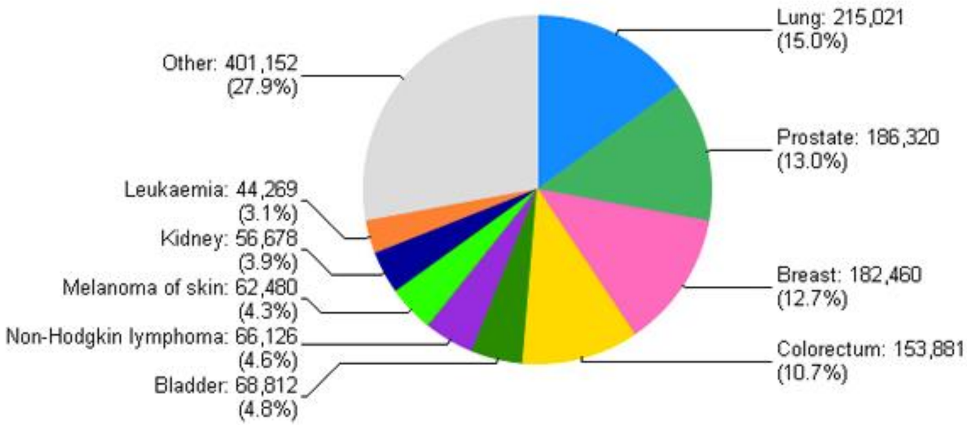
Will you or your child have a *future* health problem related to 1,4 Dioxane?

- No exposure, no risk
- Exposure, no matter at what level, does NOT mean you will have a health problem.
- *Possibility(risk or chance)* of future health problem related to
  - Dose
  - Susceptibility
  - Other exposures
  - Lifestyle
- *All of us* will have future health problems including cancer, reproductive problems, and other diseases whether or not we have ever been exposed to 1, 4 Dioxane

Dartmouth-Hitchcock

Cancer Risk

- Many of us (39.6%) will be diagnosed with cancer at some point in our lifetime
- Think of "cancer" like "infection"
  - Many different types of cancer
  - Many different causes



Estimated number of Male and Female Cancer cases in 2011 in the United States of America. 1,437,199

Dartmouth-Hitchcock

Our Lifetime Risk of Cancers

- Kidney
  - 39 new cases per year per million people
  - 17,000 per 1 million lifetime risk
  - 1 excess case = 17,001
- Liver
  - 82 new cases per year per million people
  - 9000 per 1 million lifetime risk
  - 1 excess case = 9001

Another, very real problem

- Stress and worry
- Notification that you live in a community abutting or near a hazardous waste site creates very real, and understandable worry, aggravated by uncertainty

Dartmouth-Hitchcock

What Can You Do?

- Keep up to date with Dartmouth and State information posted on websites, delivered in meetings and other communications
- Report your concerns and questions to the community health advisory group or to Maureen O'Leary
- Learn about how to reduce exposure to other hazardous environmental chemicals and agents common in our communities and homes

What Can You Do?

- Get routine health maintenance exams and live a healthy lifestyle
- Talk to your PCP if you are worried
  - OK to give him/her my name and number (603-653-3850)

Dartmouth-Hitchcock

Obstacles to a Meaningful Community Health Study

- Number of people in community is very small
- Many people from community are no longer here
- Symptoms and diseases *potentially* caused by 1,4 dioxane are common
- Only a handful of people known to have any exposure to 1, 4 dioxane from waste site
- Most everyone has some exposure to consumer products containing 1,4 dioxane and thousands of other chemicals
- Current likelihood of
  - Kidney, Liver, or nasal injury extremely remote
  - Cancer risk very low, in range of 1 excess cancer in range of 100,000 to 1,000,000 people

Other Obstacles to a Meaningful Community Health Study

- Cross-sectional study (conducted now) of people with cancer
  - Misses future cancer, which will not occur for ~ 15 years
- Retrospective study (backward looking) of people with cancer
  - People with related illness in future not counted in retrospective
  - Lack of exposure measurements in past, who was exposed and to how much?
- Prospective study (forward looking)
  - Needs to last more than 15 years to assess cancer effects from current exposures
- Any study would need to collect a great deal of information
  - Death certificates, medical records, laboratory tests of current and past workers
- Experience indicates very likely any study would be inconclusive

Questions

- With the detection limit recently lowered from ~3 to 0.25 ppb with new technology? Is it likely that the EPA/state will lower the allowable drinking water limit. At under 0.25 ppb (i.e. undetectable), is there a chance that there are adverse health effects especially on the young or elderly?
- States have set different levels to trigger mitigation
  - CA = 1.0 ug/L ; MA = 0.3 ug/L
  - I don't know NH's plan

Dartmouth-Hitchcock

Questions

- I would like to hear Dr McLellan's thoughts with regard to non cancerous brain tumors such as Acoustic Neuromas and Vestibular Shwannomas as related to 1.4 Dioxane.

Risk Factors for Acoustic Neuroma

- Genetic (NF2 inactivated)
- Neurofibromatosis
- Environmental
  - Childhood exposure to low dose radiation
  - Conflicting data
    - Cell phone use
    - Noise
  - No assoc with solvents or 1,4 dioxane that I know

Other Questions

General Resources

- ToxTown
  - Identify hazardous chemicals and their health effects in your community https://toxtown.nlm.nih.gov/
- Household Products Database
  - https://householdproducts.nlm.nih.gov/
- ATSDR Tox FAQs
  - Basic information about many chemicals http://www.atsdr.cdc.gov/toxfaqs/index.asp
- Dartmouth Website
  http://www.dartmouth.edu/~ehs/rennie.html
- Citizen Health Advisory Group

Technical Resources

- ATSDR Toxicological Profile for 1, 4 Dioxane http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=955&tid=199
- EPA Toxicological Review of 1,4 Dioxane https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0326tr.pdf
- Thomas Mohr. Environmental investigation of 1,4 Dioxane and other Solvent Stabilizers. CRC Press, 2010.

To calculate incremental lifetime cancer risk

- ILCR = Daily intake (mg/kg/d) x Cancer Slope Factor $(mg/kg/day)^{-1}$
  - Calculator available at:

http://www.popstoolkit.com/tools/HHRA/Carcinogen.aspx

Calculation of Cancer Risk [edit]

For each age interval "i", the cancer risk for exposure by a specified pathway is computed as:[3]

$$\text{Risk}_i = C \cdot \frac{IR_i \cdot EF_i \cdot ED_i}{BW_i \cdot AT} \cdot SF \cdot ADAF_i$$

Where:

C = Concentration of the chemical in the contaminated environmental medium (soil or water) to which the person is exposed. The units are mg/kg for soil and mg/l for water.

IR_i = Intake rate of the contaminated environmental medium for age bin "i". The units are mg/day for soil and l/day for water.

BW_i = Body weight of the exposed person for age bin "i".

EF_i = Exposure frequency for age bin "i" (days/year). This describes how often a person is exposed to the contaminated medium over the course of a typical year.

ED_i = Exposure duration for age bin "i" (years). This describes how long a person is exposed to the contaminated medium over the course of their lifetime.

AT = Average days. This term specifies the length of time over which the average dose is calculated. For quantifying cancer risk a "lifetime" of 70 years is used (ie, 70 years times 365 days/year).

SF = Cancer slope factor $(\text{mg/kg-day})^{-1}$

ADAF = Age-dependant adjustment factor for age bin "i" (unitless)