Cardiac Sensitization Toxicity Testing and Implications for CF_3I Risk Assessment as a Halon 1301 Replacement

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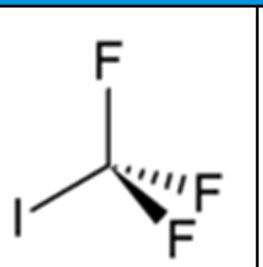
Overview

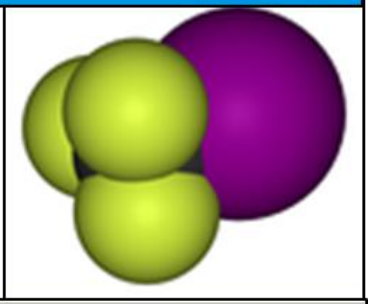
- CF_3I and Halon 1301 replacement
- Cardiac sensitization
- Standard Cardiac Sensitization Toxicity Test
- History of the development of the cardiac sensitization toxicity test
- Key toxicology concepts
- Derivation of Exposure Limits from cardiac sensitization toxicity test data
- Implication of test findings to human health risk assessment of CF_3I as a Halon 1301 replacement

Trifluoroiodomethane (CF_3I)

Boeing is evaluating trifluoroiodomethane (CF_3I) as a potential Halon 1301 replacement

Trifluoroiodomethane (CF3I)





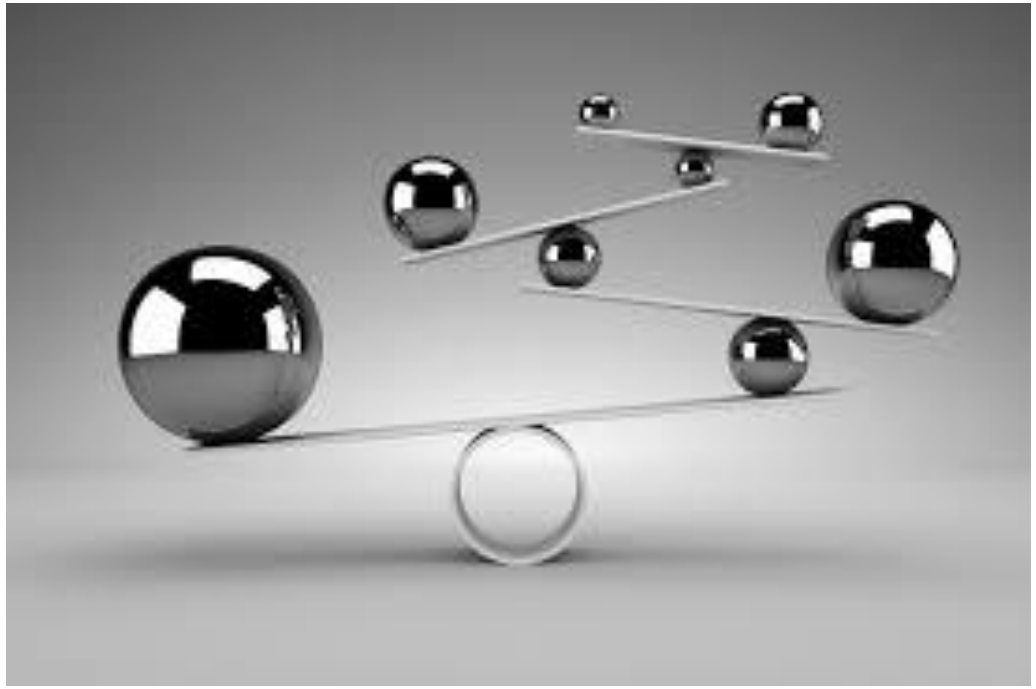
Properties	
Chemical formula	CF_3I
Molar mass	195.91 g/mol
Appearance	Colorless odorless gas
Density	2.5485 g/cm^3 at -78.5 °C 2.3608 g/cm^3 at -32.5 °C
Melting point	−110 °C (−166 °F; 163 K)
Boiling point	−22.5 °C (−8.5 °F; 250.7 K)
Solubility in water	Slightly
Vapor pressure	541 kPa

Wikipedia: CF3I

Alternatives Assessment for Halon Replacement

Challenges in balancing:

- Performance
- Design compatibility
- Health and safety
- Environmental effects
- Weight/efficiency
- Availability and cost
- Material compatibility
- Regulatory
- Many more factors…



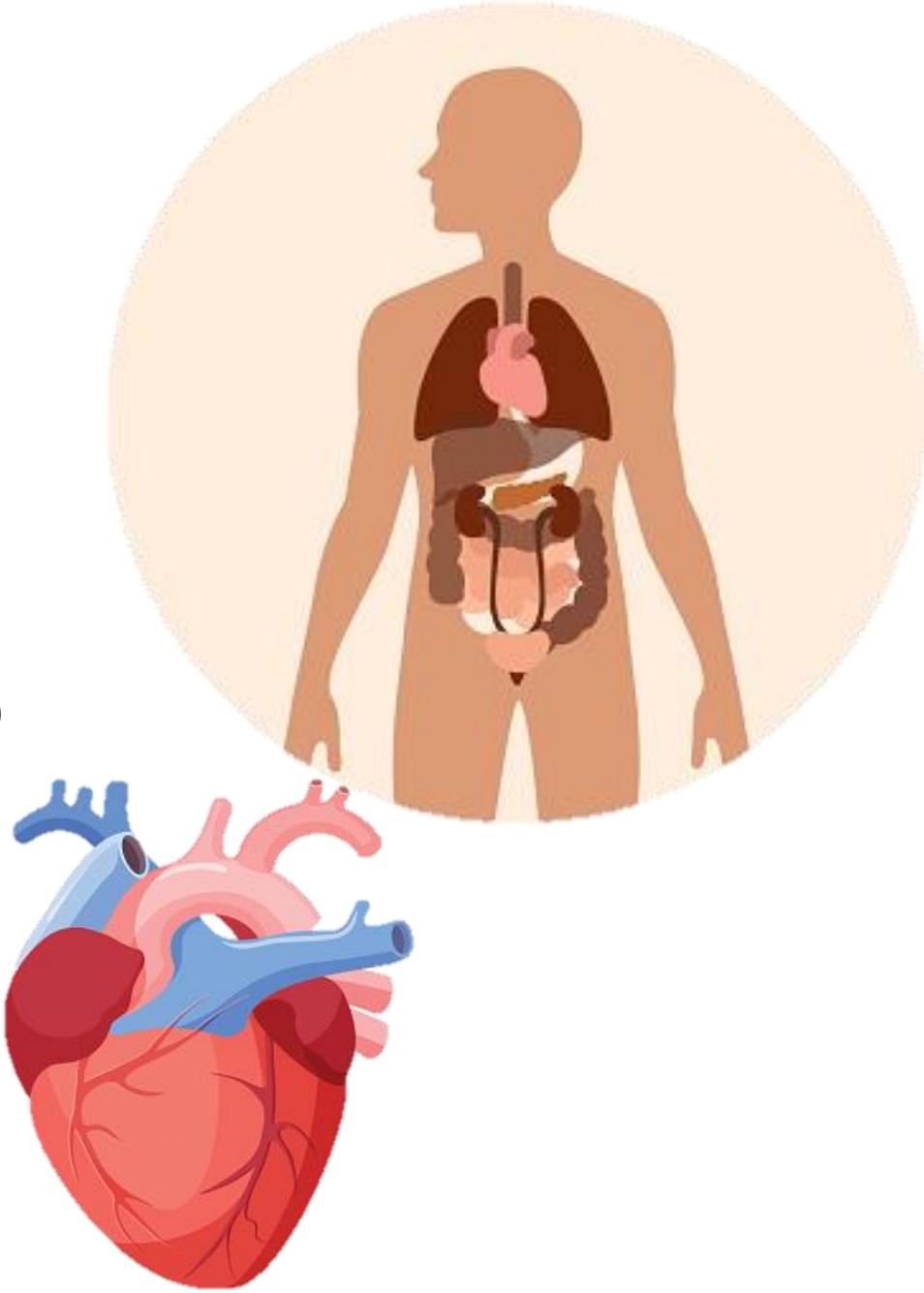
CF_3I and Cardiac Sensitization

- CF_3I has been studied as a Halon 1301 replacement for over 20 years
- The primary health effect of concern for inhalation of CF_3I is cardiac sensitization
  - Primary health effect of other halocarbons, including Halon 1301
  - Most frequently cited exposure limits for CF_3I are based on cardiac sensitization

What is cardiac sensitization?

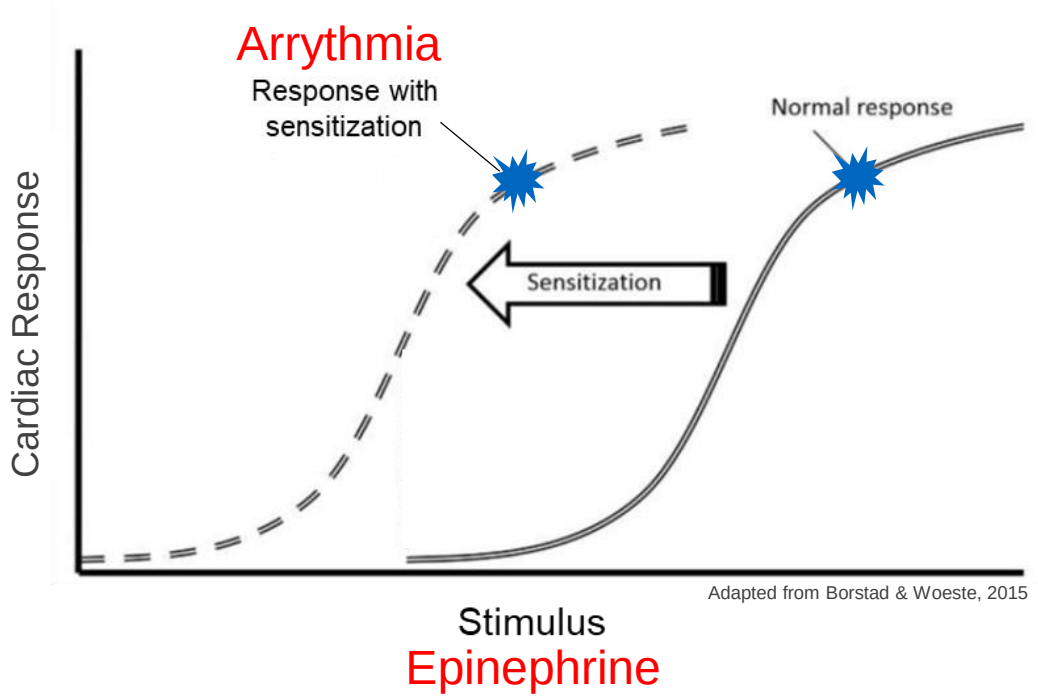
Cardiac Sensitization and the Heart

- *Cardiac* refers to the heart
- Heart’s primary function is to pump blood around the body
- Operates on specialized electrical signaling within heart for proper pump function
- Disruption of electrical signaling can cause heart to not pump correctly
- Heart rhythm problems (arrhythmias) occur when the electrical signals that coordinate the heart's beats don't work properly
- Non-functioning pump (heart) means blood can’t move around body and provide oxygen



Cardiac Sensitization

- Cardiac sensitization is an increased sensitivity of the heart to catecholamines (e.g., *epinephrine—aka adrenaline*)
  - Epinephrine can alter heart signaling– increase heart rate, strengthen contractions, etc.
- When the heart is sensitized to epinephrine, the amount of epinephrine needed to cause cardiac arrhythmias is lowered
- Cardiac sensitization may result in arrhythmias which can lead to death
- Cardiac sensitization often occurs quickly and is temporary



Adapted from Borstad & Woeste, 2015

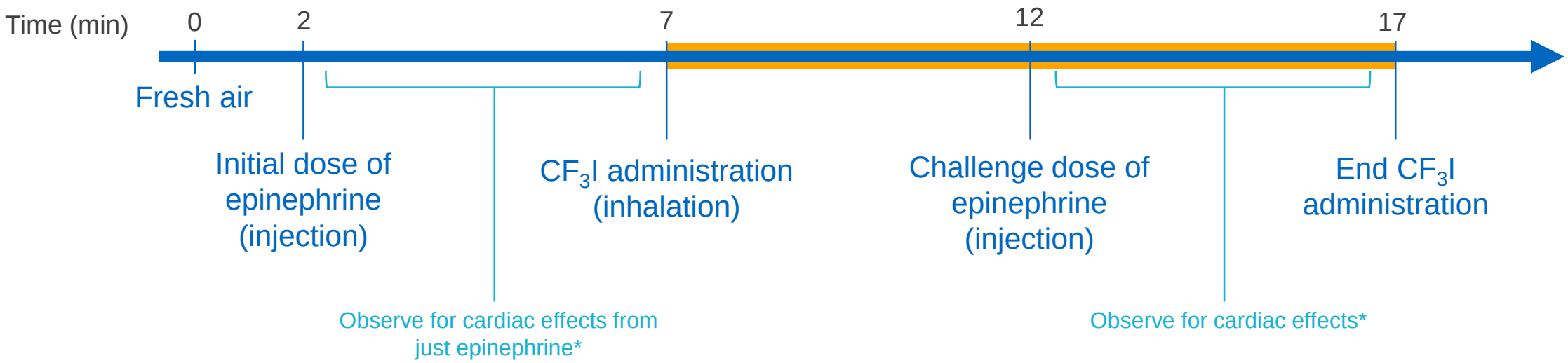
History of Cardiac Sensitization and Cardiac Sensitization Test

- Cardiac sensitization has been known to occur from inhalation of some hydrocarbons and halocarbons since the early 1900s
  - Dose at which cardiac sensitization occurs varies by chemical
- Recreational CFC propellant abuse in 1960s and 1970s–sniffing to get high resulted in cardiac sensitization
- A Cardiac Sensitization Toxicity Test was designed in 1970s to screen and rank the potential for chemicals to cause cardiac sensitization
  - Designed to elicit cardiac sensitization effect and to rank chemical potency
  - NOT designed to represent real-world exposures to chemicals, either through abuse or occupational exposure
  - “Standard Cardiac Sensitization Test”

Standard Cardiac Sensitization Test

- Toxicity test to determine whether a chemical can cause cardiac sensitization and determine level (concentration) at which it occurs
- Beagle dogs exposed to the test chemical (e.g., CF_3I) at various concentrations
- Cardiac sensitization is indicated by observation of cardiac arrhythmias

Standard Cardiac Sensitization Test Protocol



* Test is stopped if any signs of cardiac sensitization or adverse effects at any point

Cardiac Sensitization Test Goal

- Determine whether a chemical can cause cardiac sensitization and determine level (concentration) at which it occurs
  - *Determine a NOAEL (No Observed Adverse Effect Level)*
  - *Determine a LOAEL (Lowest Observed Adverse Effect Level)*
- Derive an Exposure Limit for humans

A few key toxicology concepts…

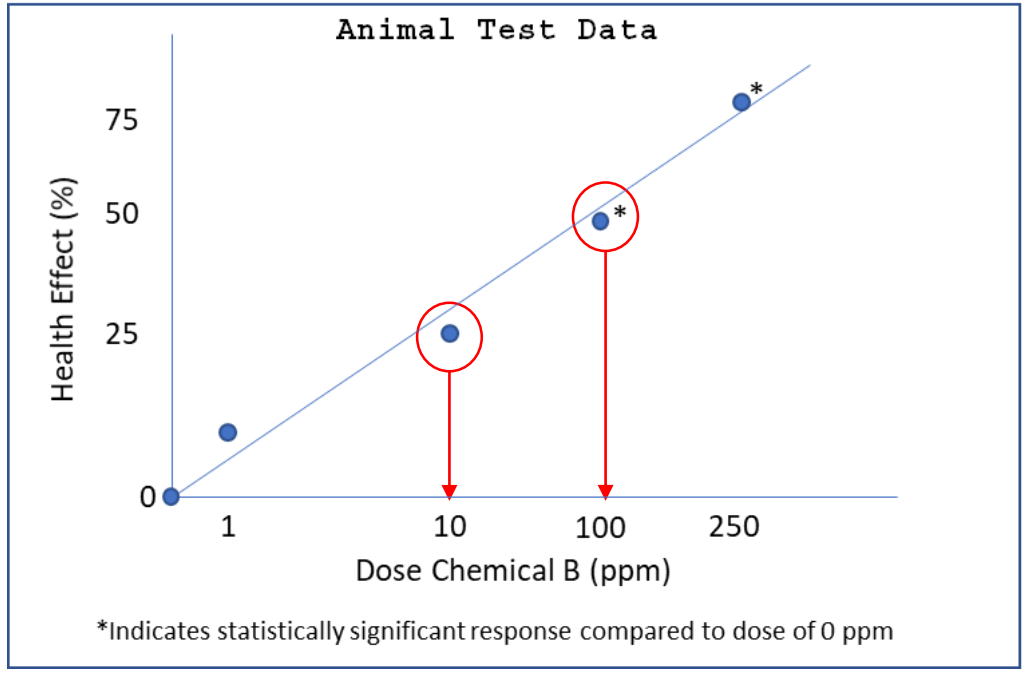
NOAEL and LOAEL

NOAEL: No Observed Adverse Effect Level

The highest dose in a toxicology study at which *no statistically significant adverse effects are observed*

LOAEL: Lowest Observed Adverse Effect Level

The lowest dose in a toxicology study at which *statistically significant adverse effects are observed*



NOAEL= 10 ppm
LOAEL= 100 ppm

Exposure Limits

Exposure Limits

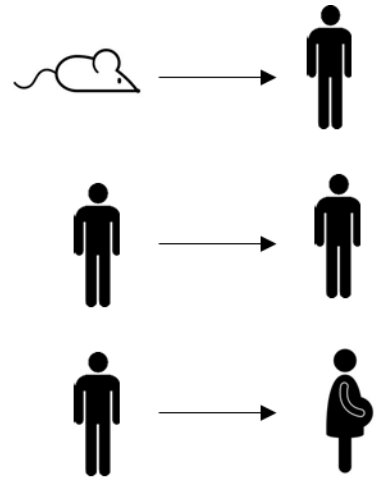
Levels at which adverse effects are not expected in humans

- Typically NOAELs are divided by *uncertainty factors* to determine Exposure Limit

$$\text{Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factors}}$$

Uncertainty Factors (UFs):

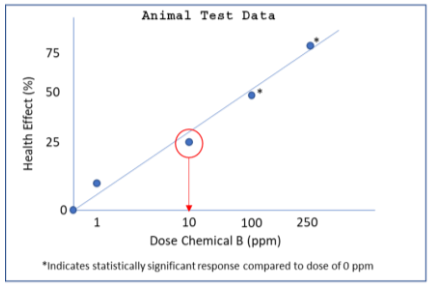
- Interspecies uncertainty: Accounts for differences between animals in tox study and humans
- Intraspecies uncertainty: Accounts for variability among humans
- Sensitive populations: Accounts for especially sensitive humans such as asthmatics or pregnant women



Uncertainty Factors:
Interspecies uncertainty= 10
Intraspecies uncertainty= 10
Sensitive populations= 10

- Not all UFs used for every Exposure Limit
- Default UF is 10, unless other data exist that show otherwise
  - E.g., data that show humans are 3x more sensitive to a certain chemical than animals would use an UF of 3 instead of 10

Example Exposure Limit Derivation



Chemical B tox study shows NOAEL of 10 ppm in rats

$$\text{Chemical B Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factors}}$$

$$\text{Chemical B Exposure Limit} = \frac{\text{NOAEL}}{10 \times 10 \times 10}$$

Uncertainty Factors:
Interspecies uncertainty= 10
Intraspecies uncertainty= 10
Sensitive populations= 10

$$\text{Chemical B Exposure Limit} = \frac{10 \text{ ppm}}{1000} = 0.01 \text{ ppm}$$

Standard Cardiac Sensitization Test

- Toxicity test to determine whether a chemical can cause cardiac sensitization and determine level (concentration) at which it occurs
- Designed to elicit the cardiac sensitization effect and rank potency
  - Uses injected epinephrine
- NOT designed to represent real-world exposures to these chemicals, either through abuse or occupational exposure

Application of the Standard Cardiac Sensitization Test

- The Standard Cardiac Sensitization Test uses an injected dose (exogenous) epinephrine to elicit cardiac sensitization effect
- The amount of exogenous epinephrine used in this test is 10x greater than the amount of epinephrine that could be generated naturally in the body by fright or exercise (endogenous)
- Cardiac sensitization occurs at lower concentrations with exogenous epinephrine
  - Less chemical needed to elicit the effect
  - Test using exogenous epinephrine will show effect at lower doses (lower NOAEL)
- Related to history of development of the Standard Cardiac Sensitization Test goal of screening/ranking chemicals
- Using exogenous epinephrine-based Standard Cardiac Sensitization Tests of chemicals don't directly translate to "real world" scenarios or risks to humans

*Exogenous- from a source external to the body (e.g, injected)
*Endogenous- produced naturally within the body

Determining an Exposure Limit for CF_3I using the Standard Cardiac Sensitization Test

Exposure Limit for CF_3I

- CF_3I has been shown to cause cardiac sensitization
- Need a CF_3I Exposure Limit for humans for safety
- Standard Cardiac Sensitization Test performed for CF_3I (Dodd & Vinegar, 1998)
- Exposure Limit currently referenced for CF_3I in Fire Protection Systems is the NOAEL from the Standard Cardiac Sensitization Test (0.2%)

Current CF_3I Exposure Limit

$$\text{Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factors}}$$

X 10 for exogenous epinephrine

Exogenous Epinephrine Standard Cardiac Sens Test

$$CF_3I \text{ Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factors}} = \frac{0.2\% \times \cancel{10}}{\cancel{10}} = 0.2\%$$

10 for animal to human uncertainty

Cardiac Sensitization Test with Endogenous Epinephrine

- Alternative version of the Cardiac Sensitization Test uses endogenous epinephrine (naturally produced)
  - Using fright or exercise for epinephrine challenge
- Higher doses of chemical needed to cause cardiac sensitization with endogenous epinephrine challenge (higher NOAEL)
- Endogenous epinephrine studies show 2-20x higher NOAEL for some chemicals
- Better represent “real world” scenarios

Would a CF_3I cardiac sensitization test with endogenous epinephrine result in a different, more representative human exposure limit?

not necessarily.

Comparison of Exposure Limits by Test Type

$$\text{Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factors}}$$

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injected epinephrine → ***Exogenous*** **Epinephrine Standard Cardiac Sens Test**

$$CF_3I \text{ Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factors}} = \frac{0.2\% \times \cancel{10}}{\cancel{10}} = 0.2\%$$

X 10 for exogenous epinephrine

10 for animal to human uncertainty

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epinephrine from fright/exercise → ***Endogenous*** **Epinephrine Cardiac Sens Test**

$$CF_3I \text{ Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factors}} = \frac{2\%}{10} = 0.2\%$$

10x higher NOAEL (endogenous epi)

10 for animal to human uncertainty

Summary and Conclusions

- Cardiac sensitization is the primary health effect from inhalation of CF_3I
- Cardiac sensitization can cause heart arrhythmias
- Current Exposure Limit for CF_3I (0.2%) is based on Standard Cardiac Sensitization Test which is not designed to represent “real world” exposure scenarios
  - Exogenous epinephrine- 10x more than natural amount
- Exposure Limit for CF_3I is not adjusted for uncertainty to account for 10x more epi
- Test using endogenous epinephrine better represent “real world” scenarios
- A CF_3I cardiac sensitization test using endogenous epinephrine would likely yield a similar Exposure Limit because of adjustment for uncertainty
- Existing CF_3I Exposure Limit of 0.2% can be applied for human health risk assessment for Halon 1301 replacement


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