

The Science of Air Fresheners

Part 2: From the Air to the Body

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From the Air to the Body

- Fragrances, preservatives, and carrier ingredients often irritate eye, nose, & throat. → Short Term Effects
- Eye, nose, and throat irritation can become progressively worse over time, even at low concentrations. → Time Dose Effects
- Inside the respiratory tract, multiple compounds can conspire together in the damage they cause or health risk they impose. → Synergistic Impacts
- Variability in the respiratory tracts within human beings and between humans & rats can make it difficult to define safe exposure levels. → Variable Consequences
- Compromised integrity of the respiratory tract leads to carcinogenic and mutagenic effects. → Emergent Impacts

Respiratory Impacts are highly variable among people & exposure

history

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Short-Term Health Effects The First Signs

- As volatile organic (VOC) and related compounds enter the upper respiratory tract and nasal cavity, they can irritate one or more of the three mucousal layers there.
 - Squamous, Respiratory, Olfactory Epithelia
- Many VOCs are “captured” in the upper respiratory tract in by glycoproteins and proteins found in the top layer of mucous. Here, they are transformed into more benign compounds rendering them “harmless” to underlying olfactory receptor layers as well as the lower respiratory tract.
- In addition to being uncomfortable, respiratory irritation serves as a warning flag to more serious health effects induced by longer term exposures, even at low to moderate concentrations.

Respiratory Irritation is a Clear Signal to reduce exposure (dose &

Short Term Health Effects






Most Common Respiratory Irritants in Indoor Air

| Irritant | Exposure Limit (ppm) | Irritant | Exposure Limit (ppm) |
|----------------------------|----------------------|-----------------|----------------------|
| Formaldehyde | 0.1 | Phenol | 5.0 |
| 2-Phenoxyethanol | 0.2 | Nonal | 6.1 |
| 2-(2-Butoxyethoxy)ethanol) | 0.5 | 2-Furfural | 7.0 |
| Hexanoic Acid | 0.9 | Benzaldehyde | 10 |
| 2-Ethyl-1-hexanol | 1.3 | Propanoic acid | 11.5 |
| 2-2-Ethoxyethoxy ethanol | 2.4 | Ethylacetate | 17 |
| 1,2-Propanediol | 2.4 | n-Butyl acetate | 22 |
| Pentanoic acid | 3.5 | Limonene | 24 |
| Acetic acid | 4.9 | Hexanal | 31 |
| α-Pinene | 32 | 1-Butanol | 38 |
| Total VOCs | | | |

Present in Air Care Products (according to Fragrance Materials Association of the United States)

Exposure Limit = Occupational Limit = $0.03 * RD50$ (50% decrease in respiratory rate in mice) Salonen et al (2009). Volatile Organic Compounds and Formaldehyde as Explaining Factors for Sensory Irritation in Office Environments. J of Occupational & Environmental Hygiene, vol. 6, pp. 239-247.

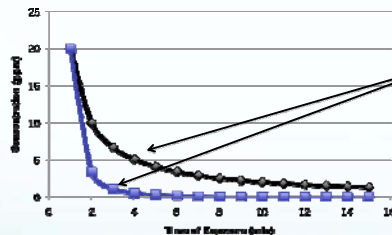
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Time-Dose Effects

A Conspiracy of How Much & How Long

- Many “ingredients of concern” cause short term health effects that are a function of both:
 - Ingredient Concentration: c (Dose)
 - Duration of Exposure: t (Time)



Combination of dose and time required to cause noticeable sensory irritation in eye, nose, or throat

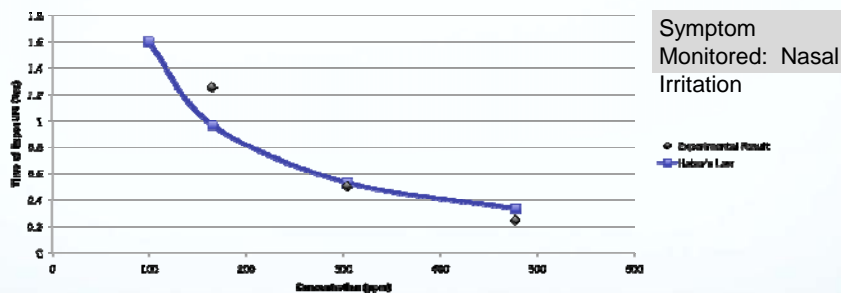
- In addition to time-dose effects, measurable irritation (ear, nose, throat) tends to plateau over time as the body adapts.

Short-term adaptation DOES NOT imply immunity from prolonged

Time-Dose Effects: Case Studies

A Conspiracy of How Much & How Long

Ammonia (common in household cleaning products)



Symptom Monitored: Nasal Irritation

◆ Experimental Result
■ Haber's Law

Because ammonia is considered an immediate danger, the trigeminal nerve responds to it. Thus, little adaptation is seen and time-dose effects follow Haber's Law fairly well.

Shusterman, Dennis, Matovinovic, Elizabeth, and Salmon, Andrew (2006). Does Haber's Law Apply to Human Sensory Irritation? *Inhalation Toxicology*, vol. 18, pp. 457-471.

Time-Dose Effects: Case Studies A Conspiracy of How Much & How Long

Formaldehyde (common in air freshener products)

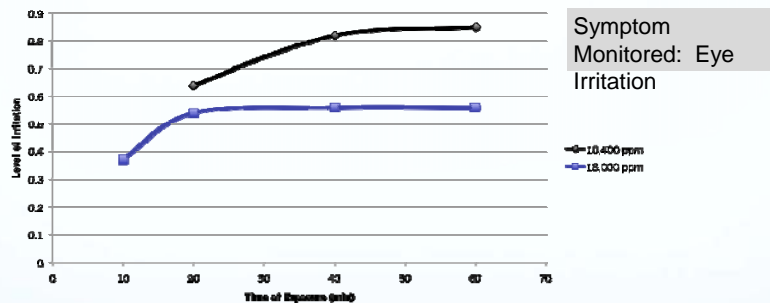
| Irritation Type | Dose (ppm) | Time (min) | Degree of Irritation |
|-----------------|------------|------------|----------------------|
| Eye | 0.5 | 10 | 0.32 |
| | | 20 | 0.38 |
| | 2.0 | 10 | 0.66 |
| | | 20 | 0.76 |
| Nose | 0.5 | 10 | 0.36 |
| | | 20 | 0.4 |
| | 2.0 | 10 | 0.88 |

Short-term irritation increases with increasing duration (time) even at small concentrations. At exposures over 20 minutes, irritation flattens out to a “saturated” level.

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Time-Dose Effects: Case Studies A Conspiracy of How Much & How Long

1-Octene (a representative VOC)



Like formaldehyde:

- Irritation in the presence of 1-Octene “plateaus over time”
- Longer exposure times enhance irritation at the same concentration, implying low concentrations can have the same effect as high concentrations if “present” long enough.

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Synergistic Effects Toxic Teamwork

Synergistic means:

Effect of Compound 1

+

Effect of Compound 2

+

· Sum or
· Near Sum
·

= Effect of all Compounds presented Simultaneously

The Problem:

Nearly all exposure thresholds are defined at individual compound levels within discrete exposure windows

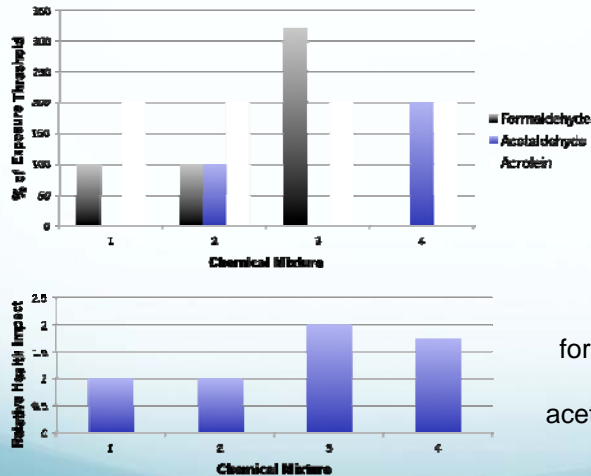
Example:
Formaldehyde
Exposure: 1 ppm
Time: 40 hrs/week

Exposure: 10 ppm
Time: 20 minutes

Fully understanding Synergistic Impacts requires looking at:
Multiple mixtures of chemicals within Multiple exposure windows

Synergistic Effects Toxic Teamwork: Case Study

The Aldehyde Conspiracy



When presented below exposure thresholds, formaldehyde and acetaldehyde do not worsen nasal lesions caused by acrolein

When presented above exposure thresholds, formaldehyde “adds” to the impact of acrolein and acetaldehyde “near adds” to the impact of acrolein

Cassee, Flemming R., John P. Groten, Peter J. van Bladerene, and Victor J. Feron (1998). Toxicological Evaluation and Risk Assessment of Chemical Mixtures. *Critical Reviews in Toxicology*, vol. 28, no. 1, pp. 73-101.

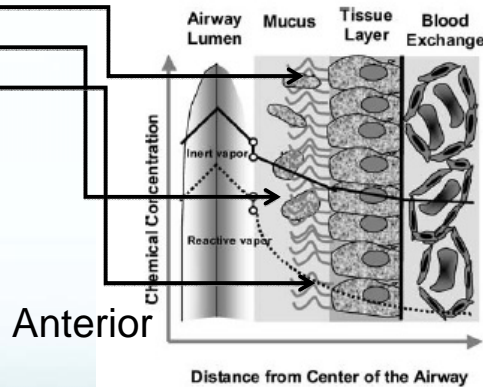
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Variable Consequences (among Humans)

- At the front end of the respiratory tract lies the nasal cavity which is covered in 3 different types of mucous:
 - Olfactory
 - Respiratory
 - Squamous

Glutaraldehyde is readily absorbed by squamous mucous. Formaldehyde is not and its absorption is concentrated in the posterior of the upper respiratory tract.



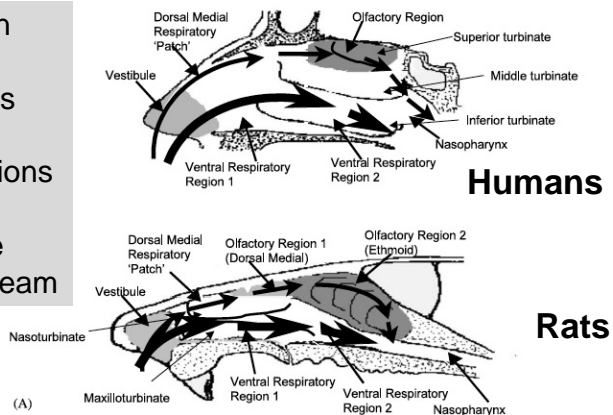
The more squamous epithelium in the mucous, the more vulnerable a person is to both the detrimental absorption of glutaraldehyde & formalde

Bogdanffy, Matthew & Sarangapani, Ramesh (2003). Physiologically-based kinetic modeling of vapours toxic to the respiratory tract. Toxicology Letters, vol. 138, pp. 103-117.

Variable Consequences between rats & humans

- Distribution of mucous is different in rats than in humans
 - (white) Respiratory Mucous/Epithelium: 46% in rats; 92% in humans
 - (dark gray) Olfactory Mucous/Epithelium: 50% in rats; 8% in humans

The olfactory mucosa can serve as a formaldehyde “sink” where glycoproteins capture and reduce net formaldehyde concentrations delivered to the more vulnerable portions of the respiratory tract (downstream of the nasal cavity)



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Emergent Impacts The Long Road to Cancer

Case Study: Vinyl Acetate

- Vinyl acetate is one of 189 hazardous air pollutants identified in the Clean Air Act.
- It is typically found in adhesives and not air fresheners

However:

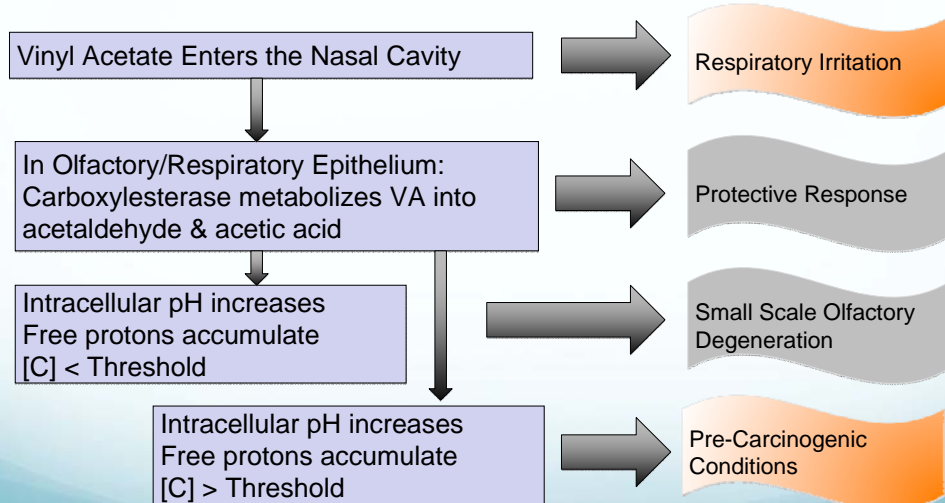
- As an organic ester, it may represent the pathways by which other organic esters detrimentally and seriously affect the human respiratory tract.
- More than five dozen different types of esters are found in air freshener products

Extracted from Aggregate Ingredients for Air Fresheners:

11/17/2008

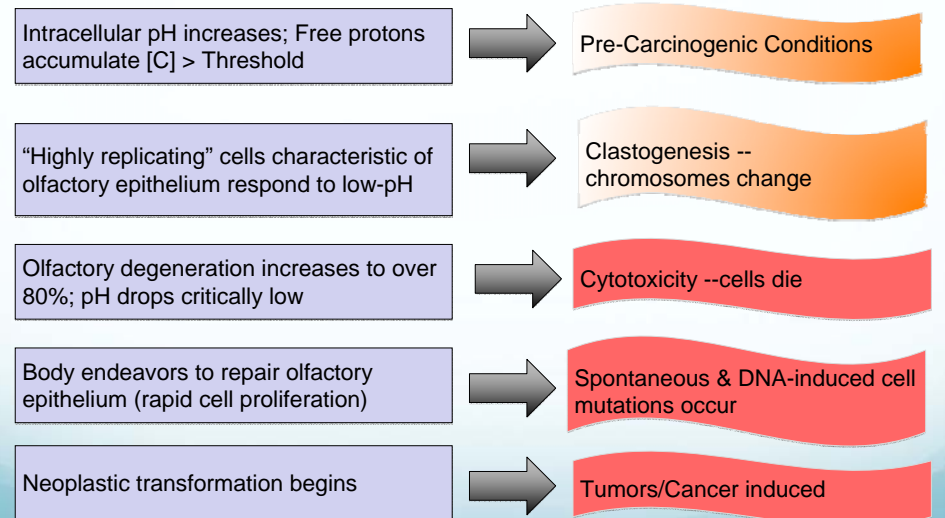
Pathways of Toxicity for Inhaled Carcinogens are Complex and Long

Emergent Impacts (Vinyl Acetate) The Long Road to Cancer



Slikker, William et al, (2004). Dose-Dependent transitions in mechanisms of toxicity: case studies. Toxicology and Applied Pharmacology, vol. 201, pp. 226-294.

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Emergent Impacts

The Long Road to Cancer

Summary: Vinyl Acetate

- As a representative (well studied) case of organic esters, vinyl acetate demonstrates the long, complex road to cancer that these compounds can induce when inhaled over long periods of time.
- Long tumor formation times (two years or more in rats) demonstrate a long causal chain that is often impossible to prove in humans.
- Dose-rate data (Haber's Law evidence) presented earlier suggests that long (chronic) exposures at moderate concentrations can produce the same biological response as higher concentrations over shorter exposure times (and ultimately the same carcinogenic impacts).

Up to a point, the human olfactory system does an excellent job of metabolizing hazardous inhalants into benign by-products. But, once overwhelmed, low intracellular pH can trigger an irreversible cancer

Conclusions

From the Air to the Body

- The olfactory system is unique -- designed to drastically augment the quality of our lives, by providing us with the pleasures that smell enables in food, drink, and other uniquely human behaviors.
- Air fresheners can convert this

Glorious Train Ride

into a

Train Wreck

Making a solid bridge between

Scientific Understanding

And

Regulation and Monitoring

A necessity to protect consumer health.

