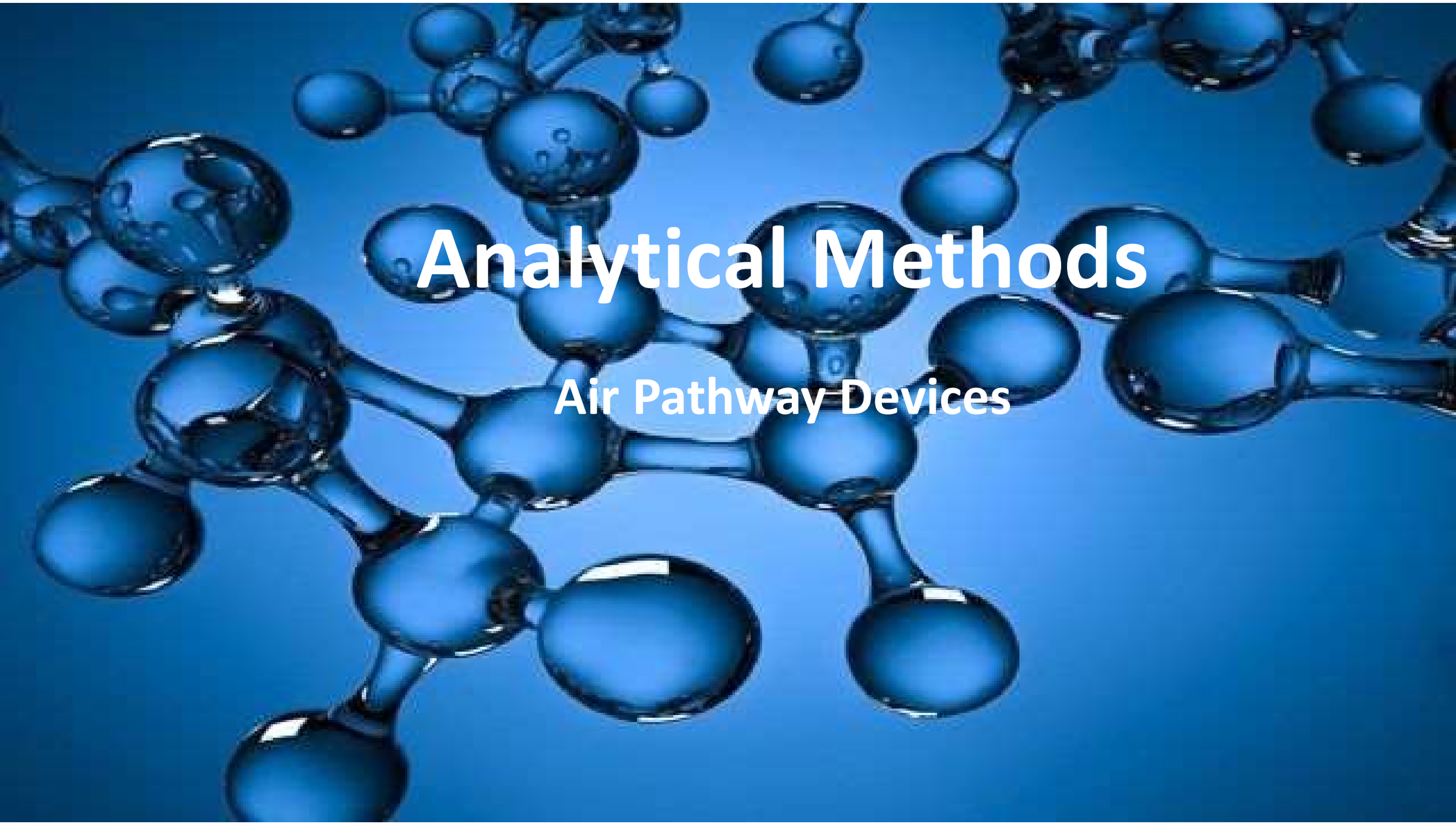
Toxicological Risk Assessment for Breathing Gas Pathway Medical Devices: ISO 10993 and ISO 18562

Russell Sloboda
Medical Device Toxicologist

Breathing Gas Pathway Devices: History of Analytical Methods

- Prior to ISO 18562, no specific guidance existed for breathing gas pathways. ISO 10993-18 considered all externally communicating devices via analysis of Extractables/Leachables (E/L) or headspace gas.
- ISO 10993-18 applies to devices that directly contact tissue or if fluids are introduced through the device into a patient. However, E/L analysis does not simulate gas-phase chemical migration.
- ISO 18562 is an FDA-recognized standard (June 2018).



Analytical Methods

Air Pathway Devices

Analytical Requirements: ISO 10993-18 vs. ISO 18562

- **ISO 10993-18**:
  - **General guidance for E/L testing**: *Polar, semi-polar, and nonpolar* solvents measure leaching of organic compounds (ISO 10993-12)
  - **Volatile Organic Compounds (VOC)** can be determined either by:

1) Analysis of aqueous extracts, or

2) Direct analysis of test article by heated headspace (90 – 115˚C)

- **ISO 18562**:
  - **E/L extraction with purified water** to simulate humidified vapor condensate (ISO 18562-4)
  - **VOC analysis by gas flow thru device** under simulated use conditions (temperature, flow rate, duration). GC/MS analysis (ISO 18562-3)
  - Particulates analysis: <2.5 µm, <10 µm (ISO 18562-2)

Two Analytical Options for VOCs by GC/MS Under ISO 18562-3

- **Thermal Desorption (TD) Method**
- **EPA TO-17 or ISO 16000-6:2011**
  - **LOQ**: ~2 ng/L (in 5L air)
  - **Accurate Range**: >C_5 to C_{20}, b.p. >50°C
  - Tube breakthrough with VVOCs
  - **Rerun/dilution possible** only if 2nd tube
  - **Reactive chemicals**: can degrade
  - **QC**: 5-pt. calibration, LCS, blanks
  - **Precision**: 12% - 25% RSD[1]

[1]Baek, SO, 2016. J. Korean Soc. Atmos. Env. 32(3): 305-319.

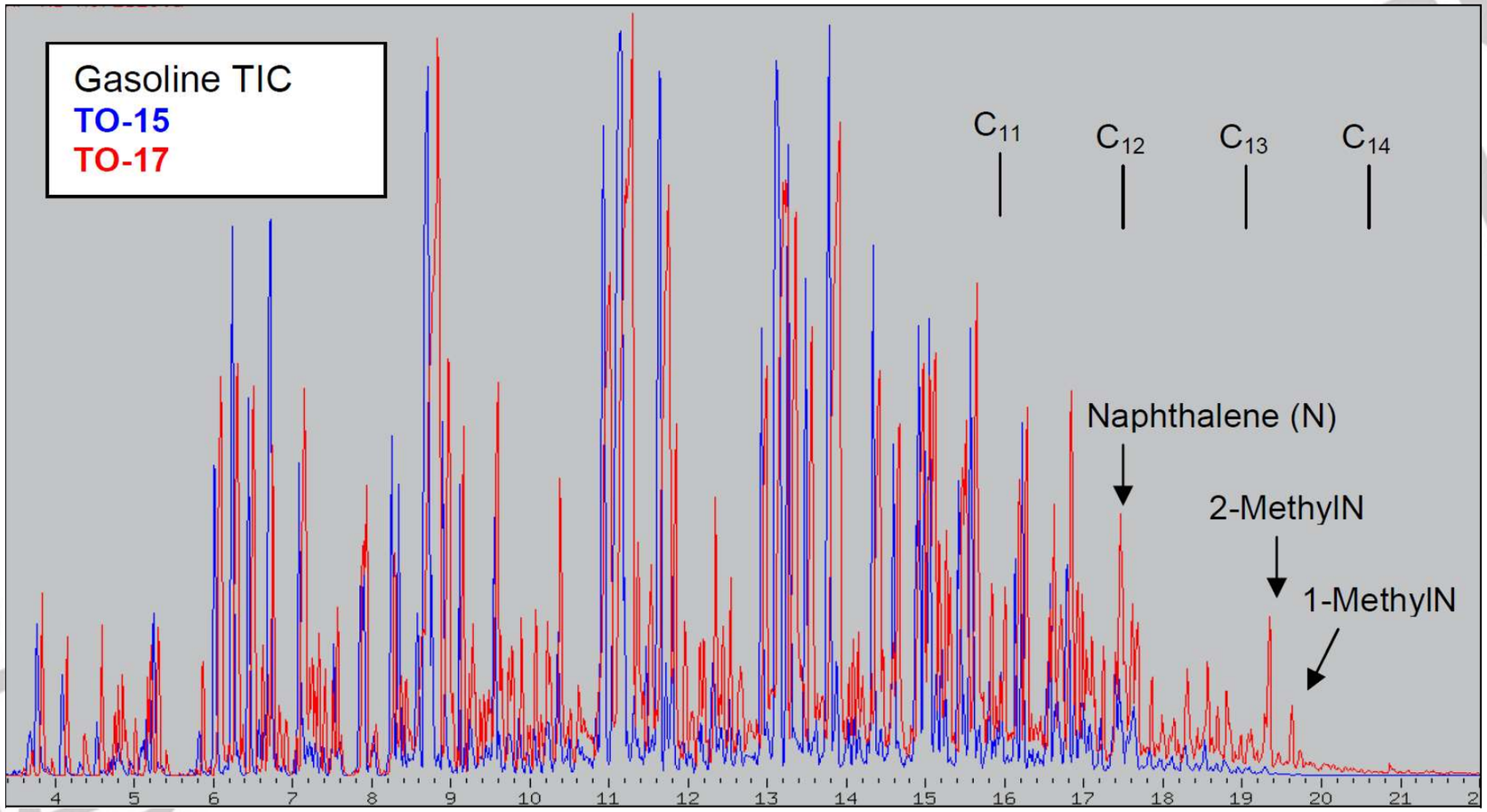
- **Stainless Steel SUMMA Canister Method**
- **EPA TO-15 or ASTM D5466**
  - **LOQ**: ~2 ng/L in 5L air
  - **Accurate Range**: C_1 to C_{11}
  - Low bias with heaviest VOCs/light SVOCs
  - **Reanalysis possible** if unused air sample
  - **Reactive chemicals**: stable if cryo-focused
  - **QC**: 5-pt. calibration, LCS, blanks
  - **Precision**: 1% - 4% RSD[1]
  - **FDA prefers TO-15**, but both TO-15 & -17 are validated EPA Compendial Air Toxics Methods

Air Sample Collection Devices for VOC Analysis: ISO 18562-3

SUMMA Canisters – 1 L to 6 L Size

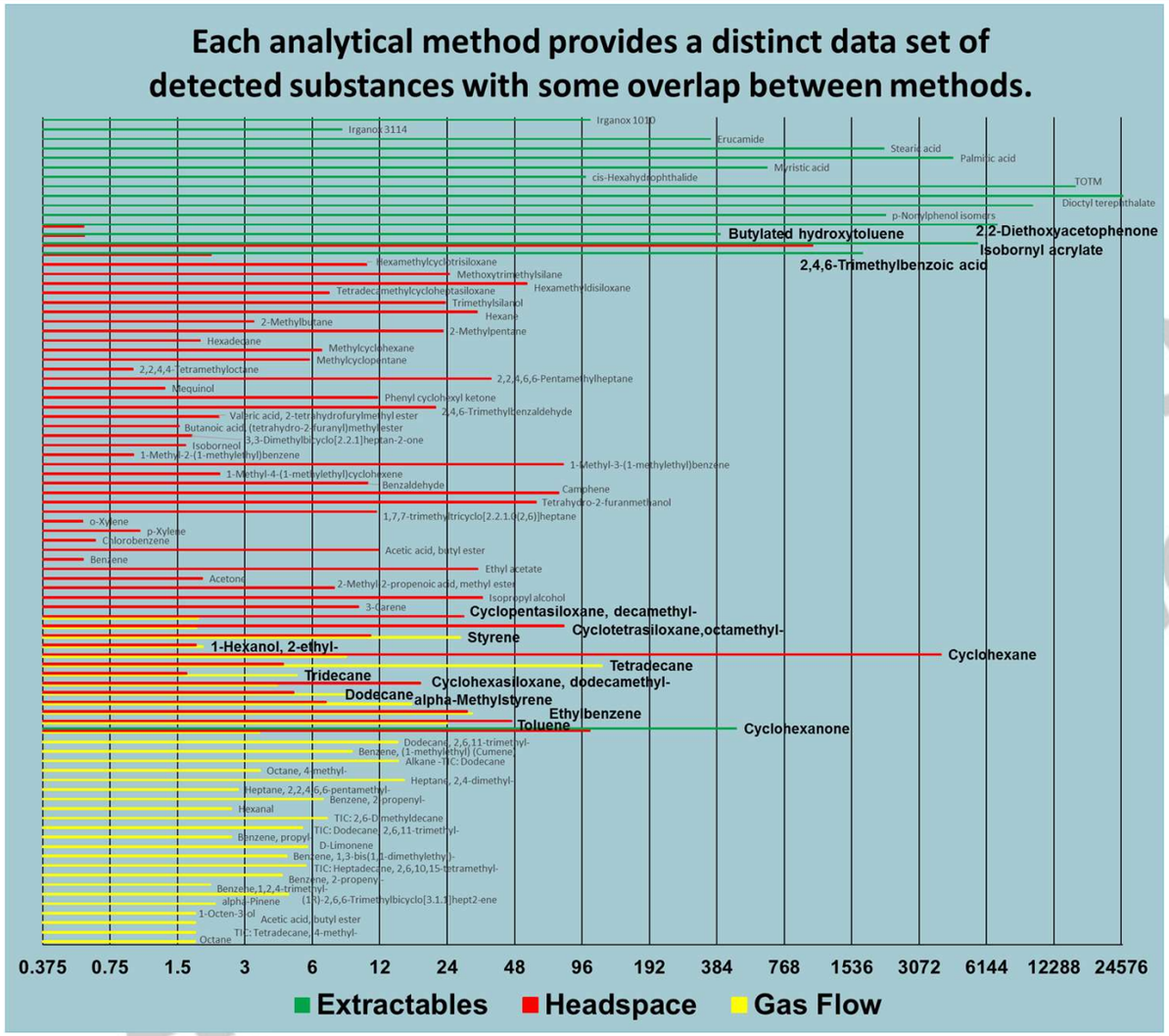
Thermal Desorption Tube

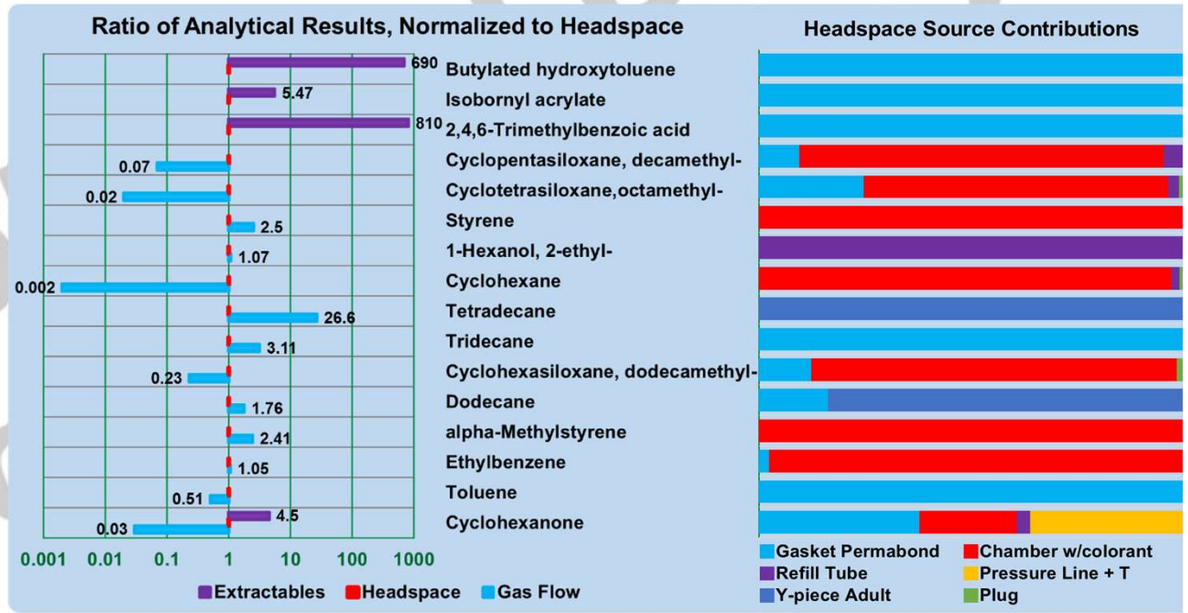
TO-15 and TO-17 Overlay Chromatograms[1]



[1] Haynes, HC, et al, 2007. Evaluation of sorbent methodology for petroleum-impacted site investigations. AWMA Conference: Vapor Intrusion: Learning from the Challenges. Sept. 26-28, Providence, RI.

Comparison of Methods: Extraction, Headspace, Gas Flow





Choice of extraction solvent affects polymer swelling and extraction of nonpolar compounds

Water is most realistic solvent to simulate humidified vapor condensate

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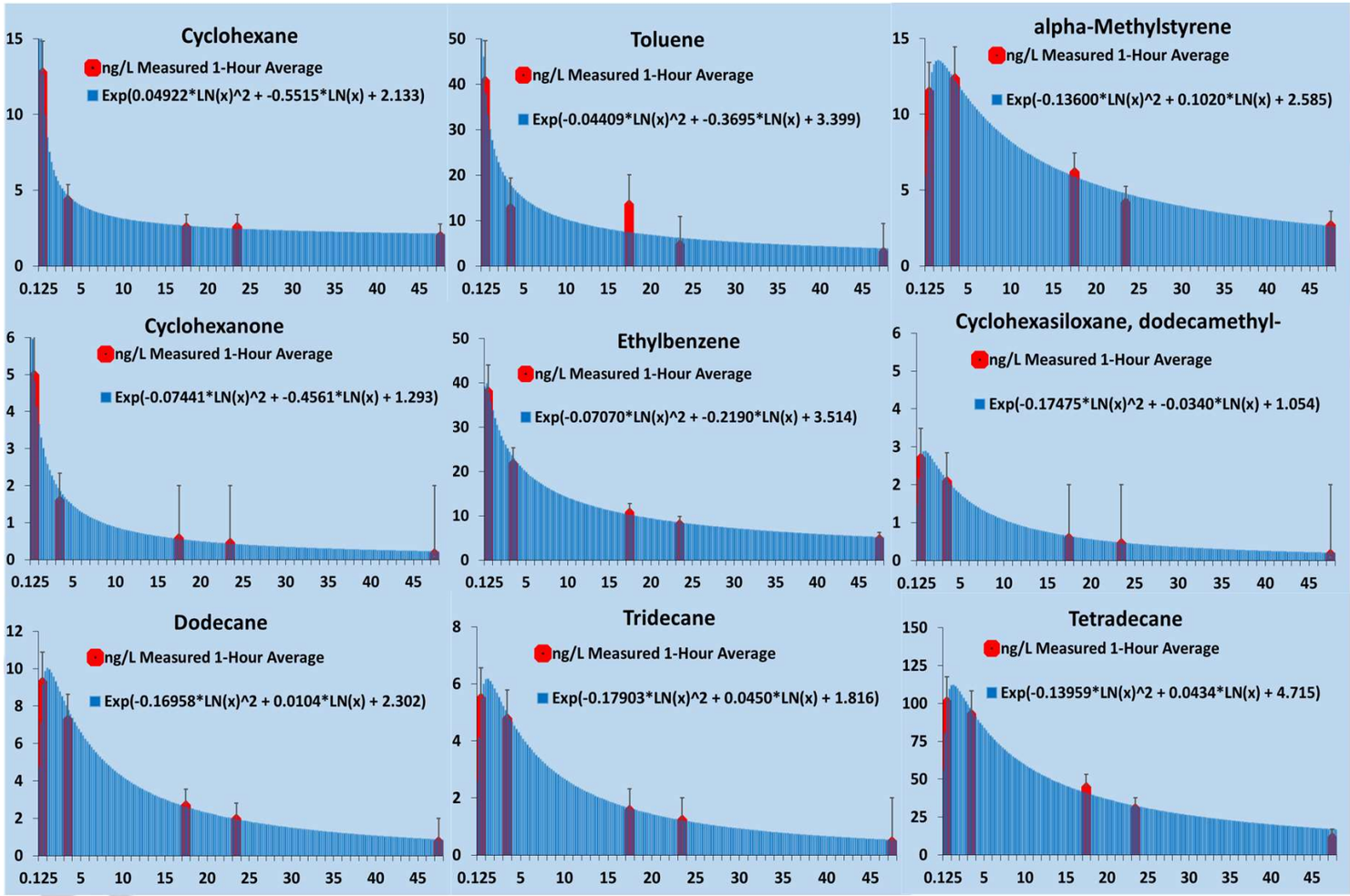
Gas Flow Pathway Analysis: Volatiles Released vs. Time

Simulated use, 48-hr. gas flow analysis by TD-GC/MS



ISO 18562 recommends sampling at intervals over the clinical duration of use

Results are used in the Toxicological Risk Assessment according to ISO 18562-1 or ISO 10993-17

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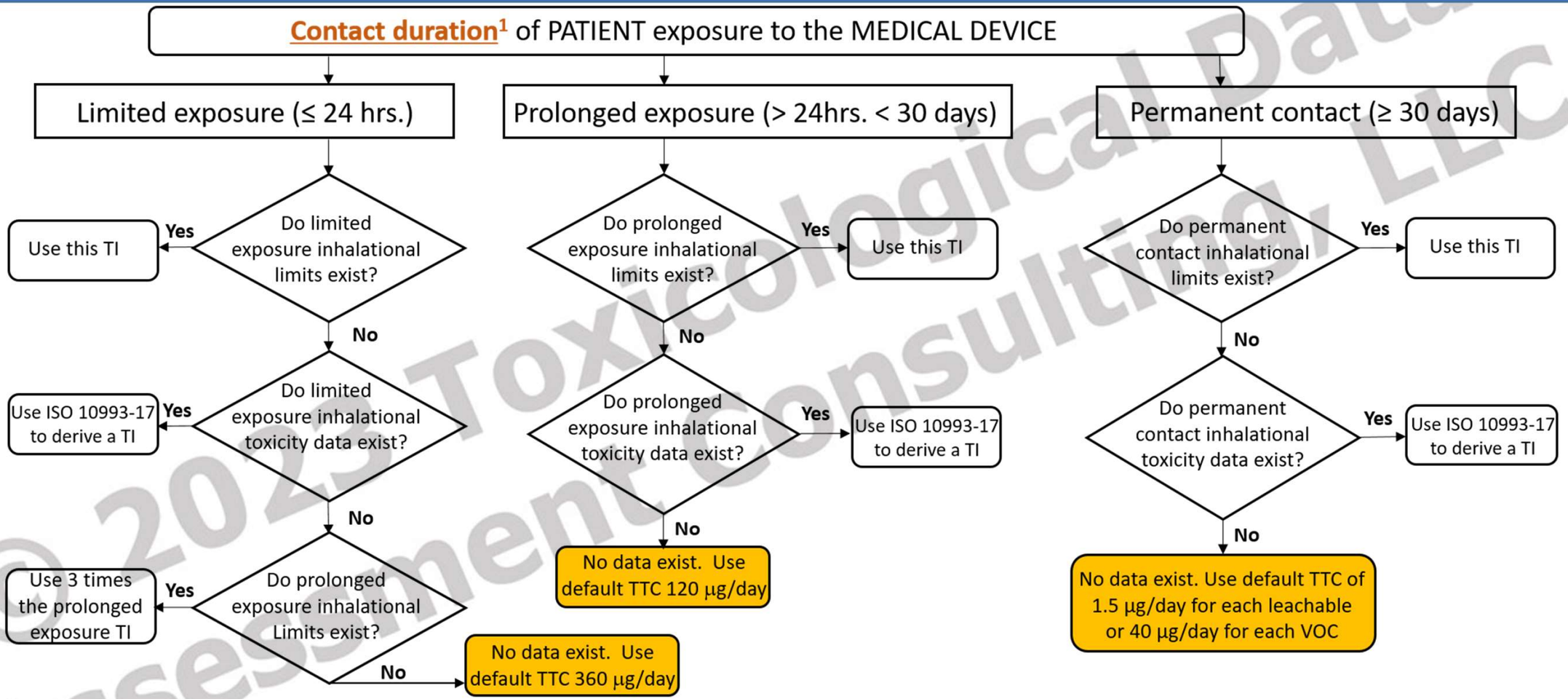
Threshold of Toxicological Concern (TTC) in 18562-1

- **TTC = Generic level below which risk is negligible, for any chemical**
- Depends on **duration of exposure**
- **ISO 18562 TTCs have some caveats** (although ISO 18562 is recognized by FDA)
- **Gas flow TTC = 40 µg/day (permanent contact)**: based on LOQ, not cancer risk Note: LOQ for E/L is lower, so must use ICH M7 SCT = 1.5 µg/day
- **Gas flow TTC = 120 µg/day (prolonged contact)**: # based on 5th percentile of NOAEL data for noncancer effects for all VOCs in RepDose. If QSAR screening is used to assign Cramer Classification, Class I/III 5% NOECs are 180 & 4 µg/day[1]
- **Gas flow TTCs for non-adult age groups** should be adjusted for breathing rate

[1] Escher, S., 2010. Evaluation of Inhalation TTC Values With the Database RepDose. Regulatory Toxicol. and Pharmacol., 58:259-274.

ISO 18562-1: Flowchart to Derive a TI for Compounds



[1] Defined as duration of exposure to original plus ***subsequent replacement devices***, not duration of use of an individual device.

Toxicity Thresholds for Inhalation Exposure

- **Tolerable Intake (TI)** and **Tolerable Exposure level (TE)**:
  - **TI: Max. dose at which adverse effects are not expected**, with a margin of safety
  - **TI (mg/m^3)** = (NOAEL or LOAEL) / Modifying Factor (MF)
  - **NOAEL or LOAEL based on 5 days/wk.**: convert to continuous exposure threshold
  - **Modifying Factor (MF)** consists of Uncertainty Factors: MF = ($UF_1 \times UF_2 \times UF_3$)
  - **TE (mg/day)** = TI (mg/m^3) × (m^3/day breathing rate*) × (UTF)

*70kg adult (20 m^3/day), 10kg child (5 m^3/day), 3.5kg infant (2 m^3/day), 0.5kg neonate (0.21 m^3/day)

Risk Assessment Approach to Extractables for Air Pathway

- **Aqueous extract**: For estimating inhalation of vapor condensate
- **Nonpolar extract**: Only relevant if device **contacts tissue**
- **Semi-polar** (alcohol/water): **Tissue contact** or **drug delivery aerosol**
- ISO 18562: Condensate exposure presumes 1 mL of extract inhaled/day
- **FDA does not recognize 1-mL condensate model**; require justification
- **Worst-case assumption**: Assume *entire* extract = condensate inhaled
- Calculate 1 mL & worst-case exposure (even 1 mL can be overestimate). Alternatively, conduct a residual moisture condensate simulation.[1]

[1] ISO 9360-1: Anaesthetic and Respiratory Equipment, Heat and Moisture Exchangers for Humidifying Respired Gases

Case Studies

Air Pathway Devices

Case Study: Resuscitator Delivery System and Face Mask

- **Oxygen delivery system**: Intended for neonates & infants
- **Passive humidification**: moisture in exhaled air recirculates
- **E/L Analysis**: 72-hour extraction (water and 20% ethanol) data used to estimate release of leachables in clinical use
- E/L conducted on components that may contact exhaled air
- **Emissions of VOCs and particulates** measured for gas flow pathway
- **Summa air canister samples** collected at 3 intervals over a 24-hour period (initial, midpoint, & end-of-period)

Case Study: Resuscitator Delivery System, Continued

- **Exposure model**: **Humidified vapor condensate** (water extract)
- ISO 18562 calculation would use 1 mL of extract = vol. of vapor condensate inhaled, *but FDA required justification for model*
- **Residual moisture test** (per ISO 9360-1) conducted at time points of 1, 2, & 6 hours: **Maximum vapor condensate = 0.09 ml**
- **(µg/ml extract) × (0.09 ml) = µg/day**
- Exposure is a *very small fraction* of extract

Compounds	Extractable Amount (µg/mL)	Potential Exposure (µg/day)
Acetone	0.0269	0.00242
Isopropyl Alcohol	0.128	0.0115
Methylene Chloride	0.389	0.0350
2-Butanone	0.0309	0.00278
Methyl methacrylate	0.0321	0.00289
Cyclohexanone	0.346	0.0311
1,2,4-Trimethylbenzene	0.0874	0.00787
2-Ethyl-4-methyl-1-pentanol	0.0377	0.00339
4-Hydroxy-4-methyl-2-pentanone	0.001	0.00009
Cyclohexanone	5.15	0.464
2-Butoxyethanol	0.069	0.00621
2-Ethyl-1-hexanol	0.513	0.0462
Acetophenone	0.239	0.0215
Isophorone	0.062	0.00558

Case Study: Resuscitator Delivery System, Continued

- **Exposure model: VOC emissions**
- **µg/day intake = µg/m³ maximum air conc.** x breathing rate (**2, 5, 20 m³/day**)
- **Exposure duration**: Worst-case 6-hours total exposure **(µg/day) x (6 hrs./24hrs)**
- Several values not > 3X ambient air blank (*)
- Data for Target Compounds (TICs not shown)

Compounds	Emission Level (µg/m³)			Exposure Level (µg/day)		
	0-3 hours	10.5-13.5 hours	21-24 hours	Infant	Child	Adult
Ethanol	18*	8*	11*	9	22.5	90
Acetone	360*	310*	210*	180	450	1800
Carbon disulfide	110*	140*	100*	70	175	700
Isopropyl alcohol	12*	7*	9.9*	6	15	60
Methylene chloride	71*	24*	77*	38.5	96.3	385
n-Hexane	9.8*	2.6*	8.5*	4.9	12.3	49
2-Butanone	2.5*	2.4*	2.1*	1.25	3.13	12.5
Cyclohexane	<1.7*	<1.7*	2.6*	1.3	3.25	13
Benzene	29*	28*	26*	14.5	36.3	145
Trichloroethene	9.7*	4.7*	6.6*	4.85	12.2	48.5
Methyl isobutyl ketone	68*	99*	72*	49.5	124	495
Toluene	8.1	8.9	7.3	4.45	11.2	44.5
Naphthalene	9.3	12	15	7.5	18.8	75
Ethylbenzene	1.2*	1.3*	1*	0.65	1.63	6.5
m,p-Xylene	2.9*	3.3*	3*	1.65	4.13	16.5
Styrene	12	16	13	8	20	80
1,2,4-Trimethylbenzene	2.9*	3.6	3.3	1.8	4.50	18

Case Study: Resuscitator Delivery System, Continued

- **Screening Risk Assessment**: VOC TTC applied per ISO 18562-1
  - **Adult TTC of 360 µg/day** = acute toxicity threshold
  - Pediatric adjustment: TTC x (breathing rate ratio)
  - **Infant TTC** = 36 µg/day = (2.0 m^3/day) / (20 m^3/day) x 360 µg/day
- **Quantitative Risk Assessment**: Section 7.2 of ISO 18562-1:
  - **Prolonged exposure inhalation values**: Use wherever limited duration (<24 hrs.) inhalation exposure limits & toxicity studies unavailable
  - **TI is multiplied by 3** to extrapolate to acute TI

Case Study: Resuscitator Delivery System, Continued

- **1-Methylnaphthalene TE calc.:** OSHA Permissible Exposure Limit = 0.5 ppm, 8-hr. **Time-Weighted Average**
- **TWA based on intermittent occupational exposure**, so convert to a continuous exposure level:
- TWA-adjusted = 0.119 ppm = 0.5 ppm × (8 hrs. / 24 hrs.) × (5 days / 7 days)
- **Multiply TI x 3 since the TWA-adjusted is based on chronic, not acute exposure**:
- TI = 231 µg/m^3 = (0.119 ppm × 3) × (142.2 g/mole) / (24.45 m^3/1000 mole air) × (10^6 µg/g) / (MF = 9)
- Where MF = (UF_1 × UF_2 × UF_3):
  - UF_1 = 3 for greater susceptibility in general population vs. workers
  - UF_2 = 1 since TWA was developed for humans (as opposed to animals)
  - UF_3 = 3 as occupational limits often based on more severe responses (not most sensitive endpoint)
- **TE = TI × (m^3/day breathing rate) × UTF**

Infant: TE = (231 mg/m^3) × (2.0 m^3/day) × (1) = 460 mg/day
Child: TE = (231 mg/m^3) × (5.0 m^3/day) × (1) = 1200 mg/day
Adult: TE = (231 mg/m^3) × (20 m^3/day) × (1) = 4600 mg/day

Case Study: Resuscitator Delivery System, Continued

- **Isopropyl alcohol TE calc.:** Based on US EPA chronic RfC derived from 13-week chronic rat inhalation study
- **NOAEL of 1508 ppm converted to a Human Equivalent Concentration (HEC)** following EPA methodology[1]:
- HEC = 662 mg/m^3 = 1508 ppm × (60.1 g/mole)/(24.45 m^3/10^3 mole air) × (6 hrs./24 hrs.) × (5 days/7 days) × BGPC
- Where: **Blood Gas Partition Coefficient (BGPC) = (Henry's Law, Blood-air in Mice)/(Blood-air in Humans)**
- BGPC = $[(H_{B/G})_M] / [(H_{B/G})_H] = (1{,}290)_M / (848)_H = 1.5$ ← (default = 1 used when BPGC > 1)
- US EPA RfC = 6.62 mg/m^3 = (662 mg/m^3) / (100 overall Uncertainty Factor)
- **Multiply RfC x 3 ← (extrapolate from chronic to acute exposure)**:
- **TI = (6.62 mg/m^3 × 3) / (UF_1 × UF_2 × UF_3)**
- Where UF_1 = 1, UF_2 =1, and UF_3 = 1 since RfC accounts for: (1) inter-individual differences among people, (2) animal-to-human toxicity extrapolation, and (3) clinical route of administration same as reference study
- **TE = TI × (m^3/day breathing rate) × UTF**

  Infant: TE = (19.9 mg/m^3) × (2.0 m^3/day) × (1) = 40 mg/day
  Child: TE = (19.9 mg/m^3) × (5.0 m^3/day) × (1) = 100 mg/day
  Adult: TE = (19.9 mg/m^3) × (20 m^3/day) × (1) = 400 mg/day

[1] US EPA, 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F. October.

Case Study: Resuscitator Delivery System, Continued

- **TE compared to maximum daily intake** for chemicals of potential concern. Comparison expressed as a ratio, or **Margin of Safety (MOS)**

Chemical	Estimated Exposure (µg/day)			Tolerable Exposure (TE) (µg/day)			Margin of Safety (MOS)		
	Infant	Child	Adult	Infant	Child	Adult	Infant	Child	Adult
Acetone	180	450	1800	120,000	310,000	1,200,000	670	690	670
Carbon disulfide	70	175	700	12,000	31,000	120,000	170	180	170
Methylene chloride	38.5	96.3	385	3,600	9,000	36,000	94	93	94
Methyl isobutyl ketone	49.5	124	495	18,000	45,000	180,000	360	360	360
1-Hexanol, 2-ethyl-	65	163	650	2,300	5,700	23,000	35	35	35
Benzenemethanol, .alpha.,.alpha.-dimethyl-	47	118	470	1,800	5,000	35,000	38	42	74
Carbonyl sulfide	105	263	1050	7,600	19,000	76,000	73	72	73
Cyclohexane, isothiocyanato-	180	450	1800	400	1000	4000	2.2	2.2	2.2
Cyclohexanone	105	263	1050	4,200	11,000	42,000	40	42	40
Naphthalene, 1-methyl-	50	125	500	460	1200	4600	9.2	9.6	9.2

Case Study: Endotracheal Tube

- **Used in adult patients**, duration up to 10 days
- Since **direct tissue contact**, 3 solvents used (water, 20% ethanol, hexane) w/ extraction at 50°C for 72 hours
- **Exposure model**: assess leachables from mucosal tissue contact; also from contact with humidified vapor condensate
- **Compare two exposure estimates**: 1 mL extract versus entire extract
- **TTCs from PQRI[1] for parenteral exposure**: Cramer class 1 (150 µg/day), class 2 (50 µg/day), sensitizer/class 3 (5 µg/day), mutagen (120 µg/day)

[1] Paskiet, D., et al, 2013. The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Products (PODP). PDA J. Pharm. Sci. Technol. 67(5):430

Case Study: Endotracheal Tube: Exposure Compared to TE

Table 3: Potential Exposures to Extractable Organics Versus Tolerable Exposure Levels

Substance [CAS No.]	Extract Medium	Tolerable Exposure (µg/day)	Daily Exposure = 1 mL Extract / 10 days		Daily Exposure = Total Extract / 10 days	
			Potential Exposure (µg/day)	Margin of Safety (MOS)	Potential Exposure (µg/day)	Margin of Safety (MOS)
VOCs						
Tetrahydrofuran [109-99-9]	IPA	40,000	0.338	>100,000	18.4	2,200
	Water	40,000	0.0743	>100,000	4.05	9,900
Isopropyl formate [625-55-8]	IPA	89,000	4.49	>10,000	245	360
SVOCs						
Tetrahydro-2-furanmethanol [97-99-4]	Water	5,000	0.115	>10,000	6.27	800
Cyclohexanone [108-94-1]	Water	140,000	1.28	>100,000	69.8	2,000
	Hexane	140,000	2.08	>10,000	113	1,200
Isophorone [78-59-1]	Water	14,000	0.18	>10,000	9.81	1,400
Butylated Hydroxytoluene (BHT) [128-37-0]	IPA	5,800	4.17	1,400	227	26
	Hexane	5,800	5.54	1,000	302	19
Irgacure 184 [947-19-3]	IPA	110,000	5.31	>10,000	289	380
	Hexane	110,000	3.51	>10,000	191	580
Palmitic Acid [57-10-3]	IPA	250,000	2.62	>10,000	143	1,700
	Hexane	250,000	3.05	>10,000	166	1,500
Methyl 2-ethylhexyl phthalate [56166-83-7]	IPA	1,300	16.1	81	878	1.5
	Hexane	1,300	18	72	981	1.3
Tributyl acetylcitrate [77-90-7]	IPA	70,000	76.5	920	4,170	17
	Hexane	70,000	106	660	5,770	12
Butyl 2-ethylhexyl isophthalate [85-69-8]	IPA	1,300	11.4	110	621	2.1
	Hexane	1,300	12.8	100	698	1.9
Bis(2-ethylhexyl) phthalate (DEHP) [117-81-7]	IPA	42,000	1,280	33	69,600	0.60
	Hexane	42,000	1,320	32	71,700	0.59
Bis(2-ethylhexyl) terephthalate (DOTP) [6422-86-2]	IPA	18,000	150	120	8,180	2.2
	Hexane	18,000	760	24	41,400	0.43
Bis(2-ethylhexyl) isophthalate (DOIP) [137-89-3]	Hexane	1,300	8.8	150	480	2.7
Tris(2-ethylhexyl) trimellitate (TOTM) [3319-31-1]	IPA	70,000	12.1	5,800	660	110
	Hexane	70,000	24.1	2,900	1,310	53

Potential Exposures to Extractable Organics Versus Tolerable Exposure Levels

Substance [CAS No.]	Extract Medium	Tolerable Exposure (µg/day)	Daily Exposure = 1 mL Extract / 10 days		Daily Exposure = Total Extract / 10 days	
			Potential Exposure (µg/day)	Margin of Safety (MOS)	Potential Exposure (µg/day)	Margin of Safety (MOS)
NVOCs						
Irganox 245 [36443-68-2]	IPA	770	0.334	2,300	18.2	42
	Hexane	770	0.213	3,600	11.6	66
BHT [128-37-0]	IPA	5,800	3.5	1,700	191	30
	Hexane	5,800	6.69	870	365	16
Palmitic Acid [57-10-3]	IPA	250,000	8.71	>10,000	475	530
	Hexane	250,000	7.03	>10,000	383	650
Stearic Acid [57-11-4]	IPA	250,000	6.89	>10,000	376	660
	Hexane	250,000	5.57	>10,000	304	820
Erucamide [112-84-5]	IPA	53,000	0.112	>100,000	6.1	8,700
Irganox 1010 [6683-19-8]	IPA	21,000	0.0468	>100,000	2.55	8,200
	Hexane	21,000	1.24	>10,000	67.6	310
Irganox 1076 [2082-79-3]	IPA	3,200	0.162	>10,000	8.83	360
	Hexane	3,200	0.116	>10,000	6.32	510
Irgafos 168 [31570-04-4]	IPA	5,800	0.134	>10,000	7.3	790
	Hexane	5,800	0.606	9,600	33	180

← **Detection of phthalates. Note a 2nd device with DEHP-free component was also tested**

Case Studies: Inhalation Drug Delivery Devices

- **Nebulizer System**:
- Humidified vapor (E/L) and gas pathway (VOC emissions) tested
- Potential chronic administration
- API usually low concentration
- **Water aerosol intake is significant**
- **Biocompatibility testing considered systemic exposure** via inhalation: cytotoxicity, sensitization, irritation, pyrogenicity, acute systemic toxicity

- **Dry product inhaler (DPI)**:
- Drug isolated inside capsule until release
- Drug contact is milliseconds; possibly too brief to interact with or leach polymer
- **Portion of device with mucosal tissue contact** (lips/mouth) required limited biocompatibility tests (cytotoxicity, sensitization, irritation)
- **Materials that contact drug product for a longer period** (drug capsule & needle) also required pyrogenicity, acute systemic tox.

Study Design Considerations

Air Pathway Devices

Optimizing Study Design

- **What device components should be tested?**
  - **VOCs and particulates**: Test all gas flow pathway components
  - **Extractables**: Components in humidified air pathway (or direct tissue contact)
- **Conditions of analysis?**
  - **Gas flow sampling**: Clinical flow rate, temperature, max. duration of use
  - **SUMMA canisters** (per FDA); collect 1 - 5L air samples at multiple intervals
  - **Extractables**: Purified water (or 3 solvents), 50°C, 72 hrs.
  - Components – **Test separately** if not same contact duration
  - **Extract analysis**: VOCs, SVOCs, NVOCs, possibly metals
  - Heated headspace analysis **not advised** (not realistic simulation)

Study Design – Key factors

- **Hexane should be avoided** if no direct patient contact:

FDA response when exposure exceeds the TE using hexane: *"Please perform additional biocompatibility testing of your device to address the non-polar chemicals that presented margin of safety values that were less than 1 from your non-polar solvent extraction of your device. Please be aware that the complete safety of your device can't be determined without additional information that indicates whether the non-polar chemicals pose a health concern."*

- **Gas flow sampling for VOCs should be at the minimum flow rate** and maximum operating temperature. Particulates at maximum flow rate
- **Extract components separately** if there are different durations of use
- **Consider separate analysis of unique accessories** designed for most vulnerable population (e.g., neonate). Different exposure calculations.

Combining Multiple Components for Extraction

- **Combining components to test as one system saves money but has drawbacks**:
- **FDA guidance for industry, ISO 10993-1**, Part F: Inclusion of Multiple Components:

  "If the components are combined into a single test article, this will dilute the amount of component materials being presented to the test system and may not accurately identify potentially toxic agents that would have been found if components were tested separately."

- **Volume of test article extracts depend on surface area** (ISO 10993 specifies 3 cm^2/mL or 6 cm^2/mL). Volume increases can be partially offset by solvent evaporation.
- **If components are extracted together**, sources of leachable analytes may be unclear.
- **FDA requires ability to detect analyte levels down to Analytical Evaluation Threshold (AET)**. Achieving AET difficult if extract volume very large - Analytes may be lost if excessive concentration of extracts by evaporation.

Combining Multiple Components, Continued

- **Representative Analysis**: For device with several sizes (e.g., child and adult), test the version with largest surface area, then toxicological risk assessment can extrapolate data to assess both devices.
- **Combined Analysis**: Combining devices yields worst-case estimate of leachables. However, simultaneous extraction increases chance of exceeding safety thresholds.
- **Hybrid Approach: Combined & Representative Analysis**: If 2 devices from same family have common components, extract one entire device plus an excised (unique) part of the other device.
- **Sensitivity of biocompatibility tests can be impaired** if several components combined for extraction. FDA may view as a test methodology deficiency.