The Role of Chemical Characterization in Biological Risk Evaluation of Medical Devices

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Key Take Aways

- Understanding the importance of the Analytical Evaluation Threshold (AET) and other aspects of Extractables & Leachables (E&L) testing
- Understanding how to work with Test Data
- Estimating Patient Exposure from Test Data
- Tips and Tricks on E&L testing and what to do if the results do not support a conclusion of acceptable patient risk
- Spotlight on assessing the risk of VOC and other contaminants detected in gas emissions testing (ISO 18562)

Definitions

- Leachable: released from a device or material during clinical use
- Extractable: released from a device or material when extracted using solvents (vehicles) and laboratory conditions
- Simulated-use extraction: extraction using method which simulates clinical use. Should be designed to produce an extractables profile that represents the worst-case leachable profile
- Component: a part or subassembly of a medical device

Toxicologists Should Play a Larger Role, Earlier On

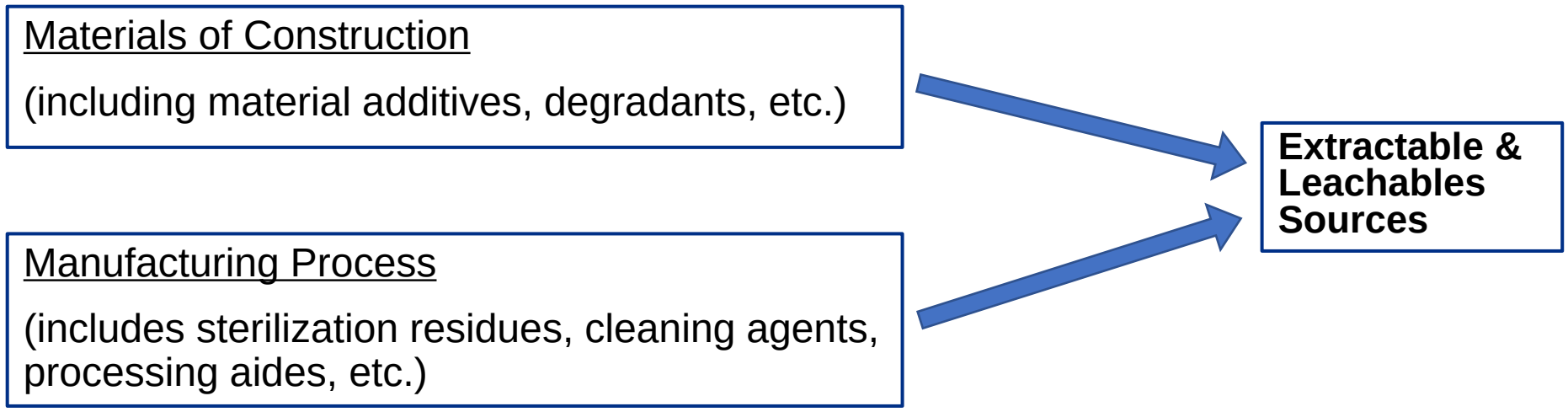
For long-term implanted medical devices, an exhaustive extraction is recommended. If an exaggerated extraction is used, then its use should be justified. It should also be recognized that if total extractables from an exhaustive (or justified exaggerated extraction) of a long-term implant medical device exceed a permissible daily exposure, the extraction kinetics (e.g. to determine maximum daily release) might need to be evaluated (e.g. by repeated analysis of a simulated extraction over time), or a leachables study performed, if possible. A toxicologist can be consulted to establish the specific data required to support risk assessment when there is a need to understand the kinetics of release.

DBT is the dose-based threshold (e.g. TTC or SCT) in µg/d (a toxicologist should be consulted in selecting a specific threshold that can support risk assessment);

ISO 10993-18:2020(E)

Risk ID & Assessment – Sources of Extractables

- Risk Assessment start with identifying the hazards and then evaluating the risks associated with exposure to those hazards.
- The toxicological risk assessment, or TRA, determines the potential of a chemical to elicit and adverse effect based on a specific level of exposure.



Extractables & Leachables Testing Aspects

- It is not possible to assess biocompatibility if the data does not adequately characterize the risk
  - Identify Hazards / Risk
    - Contact Type
    - Duration*
  - How does the device present these risks to the body?
    - Device – Patient interface / indirect / externally communicating
  - Tox risk assessment must consider the device indication and use, patient population, and route of exposure

*: duration" is cumulative patient exposure to the original plus subsequent replacement medical devices, not duration of use of an individual medical device. For example, there can be components replaced every few days so multiple sequential exposures to new replacement medical devices need to be considered.

Extractables & Leachables Testing Aspects

- What endpoints can be addressed (systemic toxicity, genotoxicity, implantation, carcinogenicity)
  - When is an implantation *study* relevant (address via testing or justification)
  - Why can cytotoxicity, sensitization, irritation *NOT* be addressed
  - Pyrogenicity testing… Others
- Methods must be sensitive enough to measure down to acceptable limit
- Chemical characterization on its own may not be sufficient to establish the equivalence or biocompatibility and doesn't unilaterally provide a substitute for biological testing
- When combined with risk assessment chemical characterization can be necessary for judging chemical equivalence and assessing biocompatibility

ISO 10993-18:2020 – Chemical Characterization

Sample selection & preparation

9 Selection of representative portions from a medical device

9.1 If a medical device cannot be tested as a whole, each individual material in the final product that is required to be tested shall be represented proportionally in the test sample.

— The test sample of the medical devices with surface coatings shall include both the coating material and the substrate, even if the substrate has no tissue contact.

— The test sample shall include a representative portion of the joint or seal, or both, if adhesives, radiofrequency (RF) seals or solvent seals are used in the manufacture of a portion of the medical device which comes into contact with patients.

9.5 Non-patient contacting portions of the medical device should, if possible, be excluded either physically from test sample extracts or by exclusion of the surface area in the calculation of the extraction ratio. When this is not possible, the extraction ratio shall be justified. Ensure that all contacting portions are covered by the selected extraction vehicle volume.

Clinician and user surface contact with materials other than those in common use in consumer products with a similar nature of contact, should be considered [see ISO 10993-1:2018, 5.2.2, a)].

9.6 Medical device components with different type or duration of tissue contact might need to be extracted and tested separately.

From ISO 10993-18:2020

ISO 10993-18:2020 – Chemical Characterization

The primary objective of the extraction is to produce an extractables profile that is at least as comprehensive as a device's leachables' profile:

- Includes all leachables as extractables
- Overestimates extractables concentration $\geq$ leachables concentrations (provides an added margin for uncertainty in the toxicological risk assessment)

Be careful to limit the extent of overestimation. Overly aggressive extractions can lead to an altered extractables' profile.

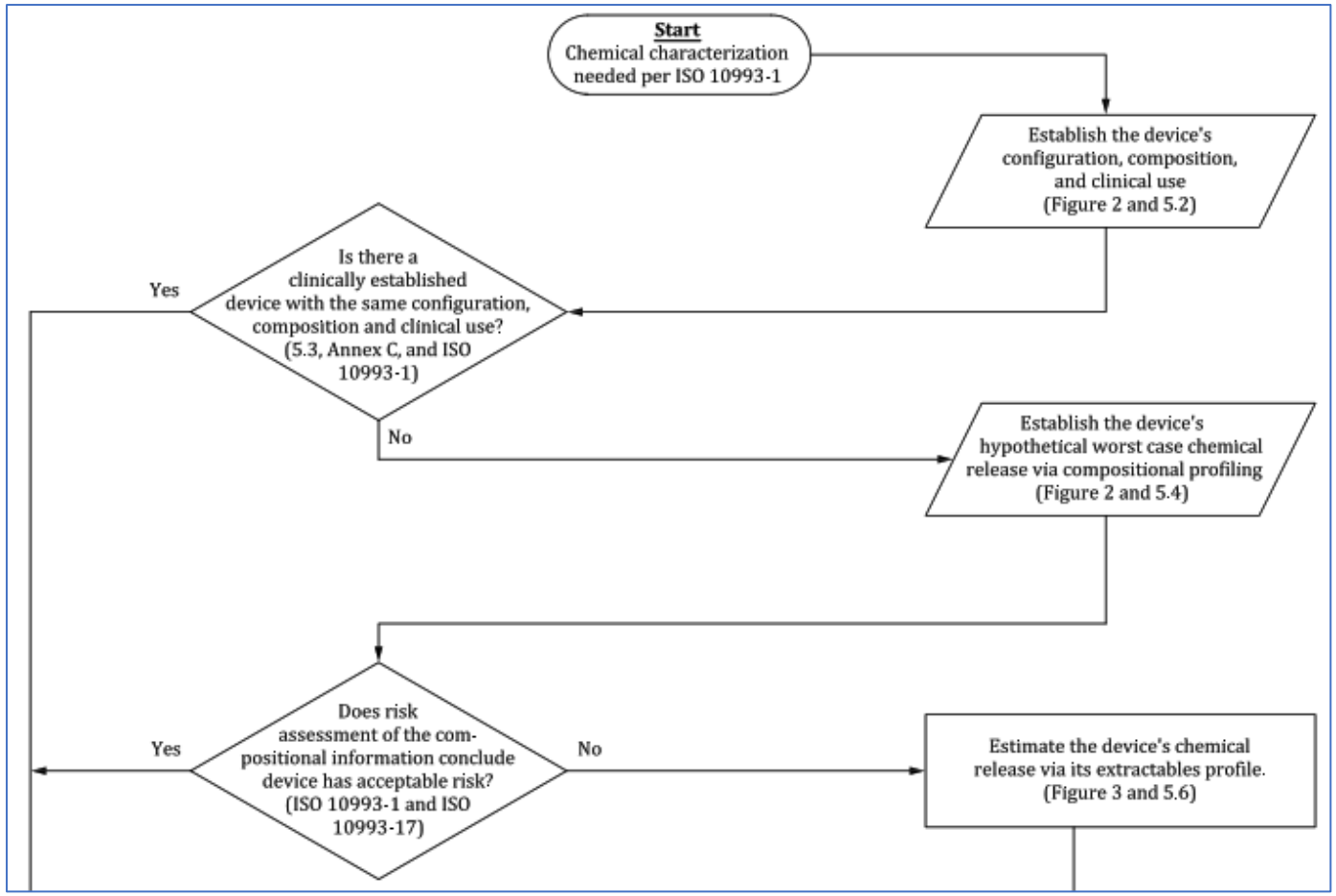
From ISO 10993-18:2020

ISO 10993-18:2020 – Chemical Characterization

When *appropriately conducted, c*hemical characterization can be used in lieu of certain biological tests, and also for things like:

- Supporting the overall biological safety of a medical device or reprocessed medical device
- Determining the amount of chemical substances that might be leached from a medical device under the conditions of its clinical use, to support performing a tox risk assessment
- Screening of potential new materials for chemical suitability
- Supporting equivalence of a:
  - Proposed medical device or material of construction to a clinically established device or material
  - Clinically established medical device, after changes in manufacturing process, sites, suppliers, etc.
  - Final medical device to a prototype device (to support use of data secured on the prototype to support assessment of the final device

Chemical Characterization Process



From ISO 10993-18:2020

Establish release via <u>compositional profiling</u> – includes potential contaminants, degradants, processing aids, and additives which could be introduced during manufacture

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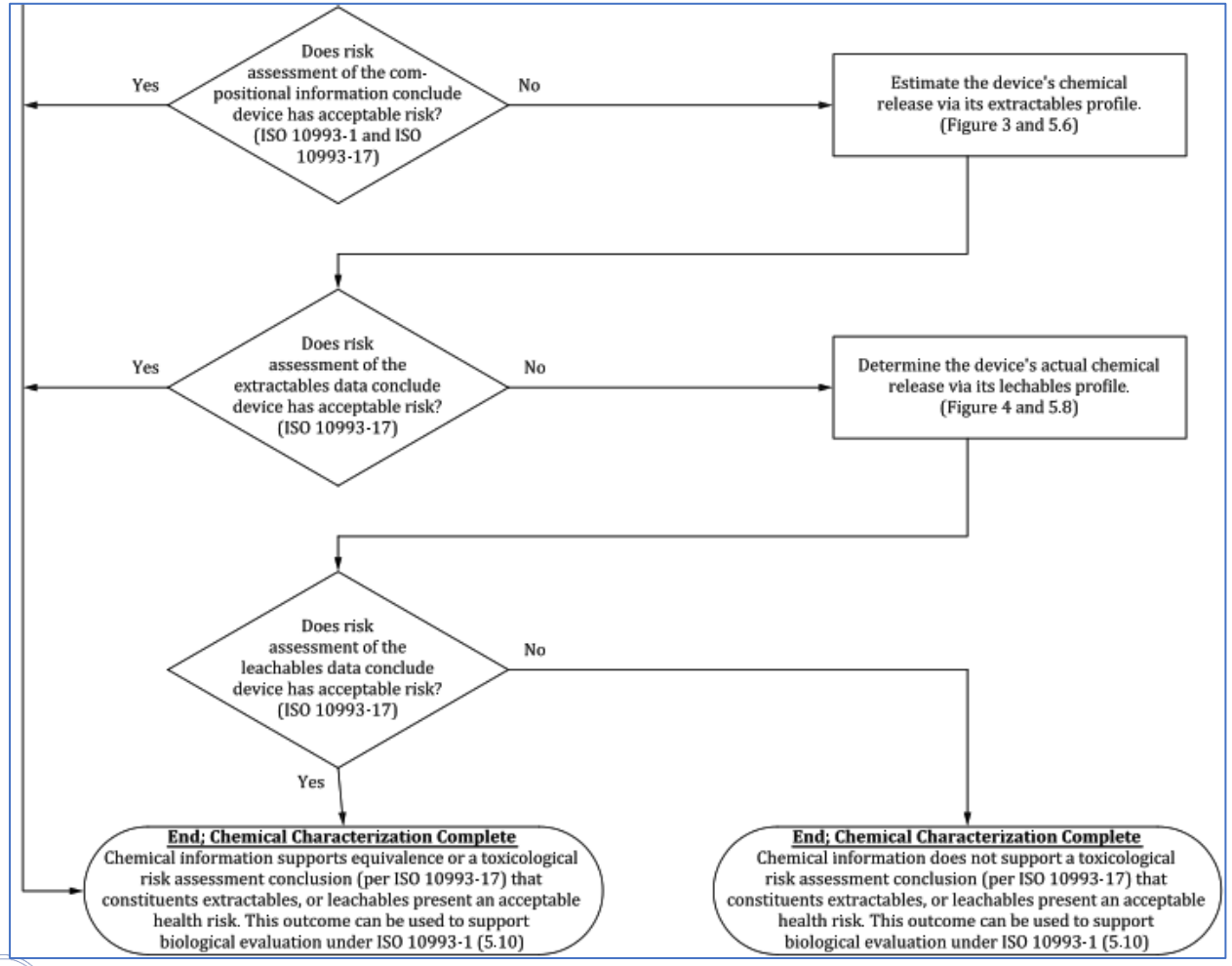
Assess adequacy as the basis for a toxicological risk assessment

↓

Does risk assessment of compositional information conclude device has acceptable risk?

Chemical Characterization Process



Estimate the device chemical release via its <u>extractable profile</u>

↓

Assess adequacy as the basis for a toxicological risk assessment

↓

Does risk assessment of extractable data conclude device has acceptable risk?

Determine the device's chemical release via its <u>leachable profile</u>

↓

Assess adequacy as the basis for a toxicological risk assessment

↓

Does risk assessment of extractable data conclude device has acceptable risk?

From ISO 10993-18:2020

Same Compound in Multiple Solvents, Components

The total level of any compound identified more than once is determined as follows:

Same compound measured in:

- More than one component (of multi-component device) → amounts are summed together

Same compound measured at:

- Same relative retention time (RRT) in different solvents → highest amount is reported
- Same RRT and same solvent (ex: replicate samples) → highest amount is reported
- Different RRTs in the same solvent → amounts are summed together
- Different RRTs in different solvents → treated separately

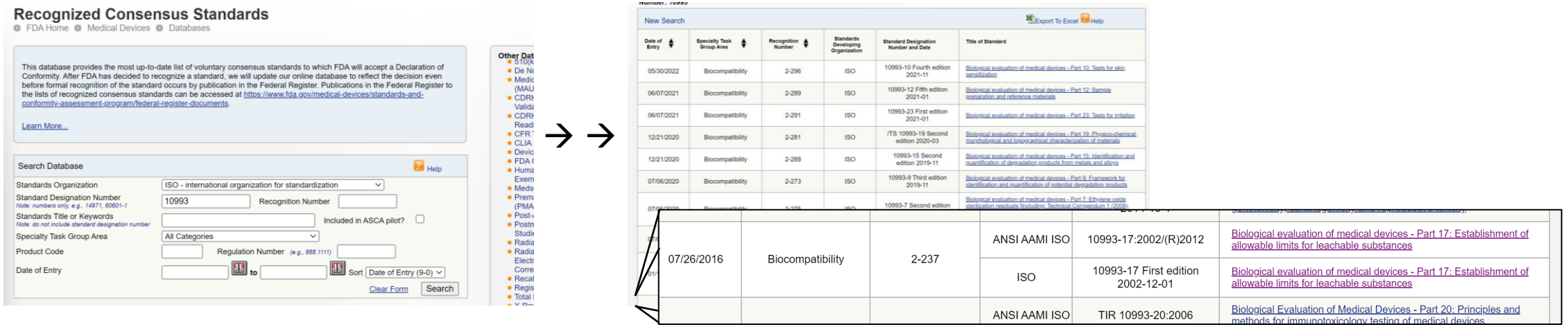
Gets complicated when there are lots of polymer fragments that differ, only slightly, across solvents

Chemical Characterization & Risk Assessment

- What's coming…
  - ISO 10993-17:2002 is current (last confirmed 2016) and a new version is in development. A draft of this is available for purchase online
    - Offers clarification of how to calculate worst case exposure of a chemical constituent

Caution on use before draft is published ….AND ….

Remember to check Center for Devices and Radiological Health (CDRH) recognized consensus standard database to see if complete or partial recognition.



Chemical Characterization & Risk Assessment

This part of ISO 10993 is not applicable to devices that have no patient contact (e.g. in vitro diagnostic devices).

Exposure to a particular chemical substance may arise from sources other than the device, such as food, water or air. This part of ISO 10993 does not address the potential for exposure from such sources.

Extent of Recognition

Partial recognition. The following part(s) of the standard is (are) not recognized:

Clause 6.2.1
Clause 6.3.2 b) 2) and Equation 6
Clause 6.3.3 and Equation 7
Clause 7.1 b) Paragraph 2, Sentences: "Economic feasibility refers to the ability to meet the tolerable exposure without making provision of the device an unsound economic proposition. Cost and availability implications should be considered in the selection of allowable limits to the extent that these impact upon the preservation, promotion or improvement of human health."
Clause 7.2, Words, either and or economically
Annex C, Clause C.2.1

Rationale for Recognition

This standard is relevant to medical devices and is recognized on its scientific and technical merit and/or because supports existing regulatory policies.
This standard is recognized in part because:
Clause 6.2.1 is in conflict with an existing published final guidance, see VI G. (pdf p. 43/68) of the guidance listed below.
Clause 6.3.2 b)2) and Annex C Clause C2.1 contains a test method that is in conflict with publish literature for extractables/leachables. See references listed below.
Clause 6.3.3 and Equation 7 contains a test method that is in conflict with published literature. See references below.
Clause 7.1 b) and 7.2 are in conflict with another recognized standard (ISO 14971 clause 6.2)

CDRH Recognition Number 2-237 (for ISO-10993-17)

2) the product of TI and m_B divided by the anticipated mean daily exposure of an average person to the leachable substance from all devices over a lifetime as given in equation (6), or

$$CEF = \frac{TI \cdot m_B}{\sum \frac{m_{life}}{25{,}000 \text{ days}}} \quad (6)$$

where

TI is the tolerable intake, in milligrams per kilogram body mass per day;

m_B is the body mass, in kilograms;

m_{life} is the mass of leachable substance releases over a lifetime, expressed as mean daily exposure in milligrams.

ISO-10993-17, Clause 6.3.2 b) 2) and Equation 6

Tips & Tricks…When outcome does not support acceptable risk

Often, the results of Chemical Characterization do not support a favorable risk assessment (too many unknowns, too many identified compounds at concentrations which exceed safe limit, etc.)

- Repeat study with different solvent, different methods, simulated use
- Perform solvent compatibility testing
- Repeat extraction for three (3) 24 hour intervals and analyze time points separately
- Fill components to expose only relevant contact area (not exterior of an indirect contact device)
- Separate components for testing
- Reconsider materials of construction

Common Pitfalls in Chemical Characterization

Reporting Limits:

- Use of an appropriate AET for organic compounds.
- Information should be provided for reviewer to check AET calculation (solvent volume, extraction ratio, # devices, etc.)
- *Must justify choice of Uncertainty Factor (UF) and Dose Based Threshold (DBT)* **
  - UF = 1/[1-(RSD)] can be used where RSD is the relative standard deviation of Relative Response Factors (RRF) of an appropriately curated response factor database (a. Diversity of chemical classes, b. Representative compounds of the extract, and c. number of compounds.)
  - Must state the Limit of Quantitation (LOQ) and Limit of Detection (LOD) for each method (these must be ≤ AET or justified)
- For elemental compounds the AET (or quantitation, reporting, detection) limit should be able to measure levels in line with the limits for elements listed in International Council for Harmonisation (ICH) Q3D guideline for the most relevant route of administration *or* derive route-specific limits

Analytical Evaluation Threshold (AET)

The duration of the medical device's clinical use could dictate the actual value used for the dose-based threshold (e.g. a staged TTC based on duration)[18] while the frequency of clinical use establishes the magnitude of clinical exposure. The AET in µg/ml can be calculated as given in Formula (E.1):

$$AET = \frac{DBT \times \frac{A}{BC}}{UF}$$

A is the number of medical devices that were extracted to generate the extract;

B is the volume of the extract (measured in ml);

C is the clinical exposure to the medical device (number of devices a user would be exposed to in a day under normal clinical practice);

DBT is the dose-based threshold (e.g. TTC or SCT) in µg/d (a toxicologist should be consulted in selecting a specific threshold that can support risk assessment);

UF is an uncertainty factor that could be applied to account for the analytical uncertainty of the screening methods used to estimate extractables' concentrations in an extract (see E.3 for a discussion on how to determine the proper value to assign to UF).

From ISO 10993-18: 2020

Common Pitfalls in Chemical Characterization

Compound ID:

- …"You have not identified all extracted compounds with a "confident" or better level. In order to accurately identify all extractables, the identification levels need to be 'Confident" or better as defined in USP
- Must describe how compounds are identified (e.g., based on best NIST library match, or based on NIST library match and fragmentation patterns as well as in house database, etc) and if identification is tentative, confident, confirmed, etc. See USP <1663>
- Report should provide as much information as possible for tentative IDs, (ex: molecular weight, molecular formula, m/z, mass fragmentation, etc.)
  - Have been seeing a lot of push back from FDA on tentative identifications requesting that further review of information be done to improve confidence of ID.
- Particulates should be characterized if present (consider FTIR, TOC, or other; depending on likely source).
- Must look for volatile, semi-volatile, non-volatile and elemental compounds. At *minimum* this will require GC/MS, LC/MS (LC/UV/MS preferred) and ICP/MS (or ICP/OES).

Common Pitfalls in Chemical Characterization (continued)

Testing Methods:

- Use of both polar (ex: water) and non-polar (or at least semi-polar) extraction solvents. **If semi-polar is used in place of non-polar then justification should be included. Solvent compatibility studies are helpful**
- Triplicate samples are highly preferred. Duplicate or pooled (several test articles) *may* be accepted. The purpose is to demonstrate control of the manufacturing process and consistent device extractable profile, and well characterized extractables (type and level)
- 50 ^{o}C for 72 hours often seen as *minimum* for extraction (unless there is REALLY good reason not to (three-24 hr cycles is acceptable and may be beneficial). Potential risk assessment approach to evaluate extract from each time point separately to provide some kinetics data)
- Describe the visual appearance of the test article in solution both before and after extraction, pictures are highly recommended
- FDA recommends that the entire volume of extraction is to be dried for NVR analysis and to determine exhaustive extraction. If only a portion or an aliquot is used for NVR analysis, provide information on the aliquot volume and percentage of the whole extract, accompanied with a justification that indicates that the sensitivity of the approach in units of mass/device is acceptable. (don't say the extraction is exhaustive based on no NVR if the sample is not sufficient to be measured.)
- Multiple (quantitation) standards (3-5) are needed for each method and multipoint calibration curves should be used. This information supports the ability of the method to measure a variety of compounds and should improve quantitation.
- Spiking is necessary when sample concentration steps or solvent exchange are performed prior to sample analysis. Use a variety of relevant standards and document procedures to show that no compounds are lost in the process.

ISO 18562 – Breathing Gas Pathway

"Gas pathway" – internal surfaces over which gas or liquid could pass.

ISO 18562, Respiratory Devices

- When a device has direct and indirect contact (ex: mask), both ISO-10993 *and* ISO-18562 can be required
- For gas pathways that can contact liquids, identify material chemical constituents and consider chemical characterization
- Evaluation of particulate matter (PM) shall be included in the biocompatibility assessment

NOTE 3 This series does not currently address BIOCOMPATIBILITY HAZARDS associated with the following substances being added to the respirable gas stream. Nonetheless, when applicable, some AUTHORITIES HAVING JURISDICTION require the MANUFACTURER to evaluate the following:

— semi-volatile organic compounds and VVOCs;

— ozone, for GAS PATHWAYS in contact with active electromechanical or electrostatic parts in NORMAL CONDITION;

— CO and CO_2, for GAS PATHWAYS where inorganic gases are generated or concentrated;

— LEACHABLES, for GAS PATHWAYS in contact with anaesthetic agents where the gas can be inspired in NORMAL CONDITION;

— LEACHABLES, for GAS PATHWAYS in contact with substances intended to be delivered via the respiratory tract (e.g. inhalational drugs).

18562-1, Section 4.5

Respiratory – Gas Emissions Testing

Externally communicating, indirect tissue contact, via the gas pathway (no direct patient contact)		WET GAS (humidity/ exhaled breath)	DRY GAS (air, medical oxygen)
	Example devices:	Circuit, inspiratory filter	ventilator
ISO-10993	Cytotoxicity	X	X
	Sensitization	X	X
	Irritation	X	X
	Acute Systemic*	X [1]	
	Material Mediated Pyrogenicity*	X [1]	
	Sub-chronic toxicity*	X	
	Chronic toxicity*	X	
	Genotoxicity*	X	
	Implantation*	X	
	Carcinogenicity*	X	
	(*) can be replaced by Extractables/ Leachables with TRA		
ISO-18562	18562-2 – Particulate Matter (PM)	X	X
	18562-3 – Volatile Organic Compounds (VOC)	X	X
	18562-4 – Leachable in condensate with TRA*	X*	
	ozone (O_3), carbon dioxide (CO_2), carbon monoxide (CO)	sometimes	

Test Methods & Allowable Limits: PM, O_3, CO_2, & CO

ISO-18562-2: $PM_{2.5}$ and PM_{10}

- Test device at the highest operational air flow rate (ex: 240 liters per minute (LPM)).
- Particulate is *continuously* monitored (measured) over a time period (ex: 240-minutes or 4 hours).
- Particulate in background air samples also recorded to confirm minimal contamination.

Ozone (O_3), carbon dioxide (CO_2) and carbon monoxide (CO) emissions

- Testing usually performed at same conditions as PM, sometime done at the same time

Measured Analyte	Allowable Limit *	References
PM < 2.5 µm	12 µg/m^3	USEPA 40CFR Part 50, National Ambient Air Quality Standard (NAAQS)
PM < 10 µm	150 µg/m^3	
CO_2	1000 ppm	OSHA Indoor Air Quality values
CO	9 ppm	40 CFR 50- NAAQS; 21 CFR 862.3220
O_3	0.050 ppm	USFDA 21 CFR 801.415

ISO-18562-3: Volatile Organic Compounds (VOCs)

If you can smell it…….

Table 4
Volatile organic compounds concentration (ppm) of essential oils at 40 °C (the heating rate was 2 °C min^{-1}) ($n = 5$).

Compounds	Rose	Lemon	Rosemary	Tea tree	Lavender	Indoor air (ppb)	Workplace air standard (ppm)
Toluene	8.89 ± 3.98	4.58 ± 0.92	8.47 ± 3.03	3.22 ± 0.22	3.70 ± 1.13	1.8–85	100
1,2,3-Trimethylbenzene	5.90 ± 0.49	5.31 ± 0.69	7.68 ± 1.12	8.37 ± 2.35	5.87 ± 2.15		25
1,2,4-Trimethylbenzene	5.74 ± 0.48	5.72 ± 1.27	14.15 ± 4.85	16.47 ± 8.11	9.13 ± 6.13	0.3–1.55	25
n-Undecane	5.59 ± 1.54	9.82 ± 0.43	10.55 ± 4.86	13.14 ± 1.77	11.97 ± 4.11	2.02–6.32	
p-Diethylbenzene	5.28 ± 0.40	6.17 ± 0.43	7.09 ± 0.74	7.91 ± 2.69	6.21 ± 1.26		
m-Diethylbenzene	5.01 ± 0.31	6.52 ± 0.71	6.84 ± 2.04	8.08 ± 1.60	6.07 ± 1.46		
n-Decane	4.19 ± 0.75	2.9 ± 0.02	3.41 ± 0.12	3.07 ± 0.03	2.51 ± 0.13	0.05–9.16	
Styrene	4.14 ± 1.48	1.77 ± 0.12	2.03 ± 0.11	2.06 ± 0.11	1.57 ± 0.04	0.14–2.56	50
1,3,5-Trimethylbenzene	3.69 ± 0.52	2.82 ± 0.18	4.95 ± 1.17	4.71 ± 1.34	3.10 ± 1.11	0.06–0.51	25
o-Ethyltoluene	3.66 ± 0.65	2.63 ± 0.12	4.62 ± 1.26	4.54 ± 1.32	3.02 ± 1.08		
o-Xylene	3.60 ± 0.88	2.29 ± 0.13	5.79 ± 2.52	6.67 ± 3.04	3.36 ± 1.53	0.41–5.62	100
m,p-Xylene	3.44 ± 0.85	2.14 ± 0.21	3.89 ± 1.20	3.58 ± 0.93	2.42 ± 0.19	0.60–14	100
m-Ethyltoluene	3.40 ± 0.70	2.46 ± 0.12	5.59 ± 2.26	5.43 ± 2.17	3.13 ± 1.34		
p-Ethyltoluene	3.38 ± 0.63	2.34 ± 0.42	4.01 ± 0.16	3.06 ± 0.74	2.37 ± 0.15		
Ethylbenzene	3.20 ± 0.95	1.79 ± 0.18	2.83 ± 0.70	2.33 ± 0.26	1.81 ± 0.10	0.21–4.88	
n-Propylbenzene	2.48 ± 0.55	1.55 ± 0.23	2.38 ± 0.41	2.31 ± 1.20	1.56 ± 0.25		
Isopropylbenzene	1.60 ± 0.35	0.97 ± 0.10	1.28 ± 0.09	1.31 ± 0.11	0.88 ± 0.12		50
n-Nonane	1.53 ± 0.37	0.91 ± 0.01	1.17 ± 0.07	1.07 ± 0.08	0.89 ± 0.15	2.29–6.39	200
n-Hexane	1.50 ± 0.47	1.26 ± 0.03	2.14 ± 0.59	2.59 ± 0.06	2.00 ± 0.14	0.79–35.6	50
Benzene	0.91 ± 0.38	0.36 ± 0.01	0.47 ± 0.12	0.42 ± 0.05	0.44 ± 0.09	0.47–10.81	5
Top 20 species (1)	77	64	100	100	72	Brickus et al., 1998; Kim et al., 2001; Sexton et al., 2004; Zhu et al., 2005; Kwon et al., 2006; Loh et al., 2006; Zuraimi and Tham, 2008; Weisel et al., 2008; Guo et al., 2009	TCLA, 2009
TVOCC (52 species) (2)	88	75	113	116	89		
(1)/(2) (%)	87	86	89	87	81		

n: five runs average.

… there are VOCs

From: Chiu, Hua Hsien et al. “Constituents of volatile organic compounds of evaporating essential oil.” Atmospheric Environment 43 (2009): 5743-5749.

ISO-18562-3: Volatile Organic Compounds (VOCs)

ISO 18562-3: VOCs

- Test at highest rated temperature & minimum operational air flow rate (ex: 40ºC & 1.0 liters per minute (LPM))

- Emissions from device sampled at time points while device is in continuous operation (ex: sampled over 7-days (168 hours) at T=0, 24, 72, and 168 hours.)
- The sample volume must be sufficient to attain a 2 µg/m^3 sensitivity.

> Common sampling durations range from 30 min to 180 min. The sampling duration chosen needs to allow averaging (e.g. of heater wire control algorithms) and smoothing of any transients in the measurement. The sampling duration might need to be longer to result in a large enough sample volume to allow quantification down to the required detection limit or reduced to prevent overloading of the sampling system. Additional sampling points are then advisable.

- Background air or source gas control samples also collected to confirm minimal contamination. Make sure it is clear if and how background levels were subtracted out

Want to be able to show a decrease in VOC levels over time

VOC Data (or PM, or Other)

So many data values…..triplicate samples, device and control, different time points….

← This is how we do it

Identified VOC Compounds		Device level (ppb) at Time Point 1						
		Device			Control Gas			Maximum Exposure (Adjusted) [c]
Name	CAS Nº.	Sample 1	Sample 2	Sample 3	Sample 1	Sample 2	Sample 3	
VOC-A	#####	14	**14**[a]	11	13	**10**[b]	12	4
VOC-B	#####	---	1.8	1	1.5	1.9	1.9	---
VOC-C	#####	2.23	2.33	**3.54**	2.58	2	**2.43**	1.11
VOC-D	#####	12	**13**	12	8	**6**	11	7

[a] Highest device level (sample 1, 2, or 3) is included in table (at each time point)
[b] Lowest control level (sample 1, 2, or 3) is included in table (at each time point)
[c] Overall maximum exposure adjusts device for control at same time point (Highest device level– lowest control level).
[(highest time 1 device – lowest time 1 control) vs. (highest time 2 device - lowest time 2 control), vs (highest time 3 device – lowest time 3 control)]

Measured concentration (ppb → µg/m³)

$\mu g/m^3$ = measured level (ppb) * molecular weight / 24.45

ISO-18562-3: Volatile Organic Compounds (VOCs)

Acceptable Limits (VOCs)

VOCs screened by comparing acceptable limit to exposure (measured) levels to determine the margin of safety (MOS).

MOS = Allowable Level ÷ Exposure Level

MOS > 1 : acceptable risk (larger MOS means less risk)

Daily exposure (inhaled dose, in µg/day) is patient population and device specific. Calculation uses the measured concentration (from device) and daily inhalation volume (DIV)

= measured concentration (µg/m^3) * daily device inhalation volume (m^3/day)

<u>Notable calculations and conversions:</u>

Daily device inhalation volume (m^3/day)

$$= \text{patient population daily inhalation volume } \left(\frac{\text{m}^3}{\text{day}}\right) * \left(\frac{\text{\# hrs device use/day}}{\text{24hr/day}}\right)$$

VOC Allowable Limit Based On:

1- Published regulatory agency values, for example:

VOC Compound	Limit (µg/m^3)	Source, Type of Value
Acetone	30,880	ATSDR, Chronic MRL
Isopropyl alcohol	200	EPA PPRTV, Chronic RfC

2- Safety assessment using available toxicity data following ISO 10993-17 methods to derive TE

3- Based on **TTC for VOCs** presented in ISO 18562-3.

NOTE: The TTC values in ISO 18562-3 are based on exposure period *AND* must be scaled down for the more sensitive patient populations.

Process to Derive Inhalational Tolerable Intake (TI) for Each Identified Compound

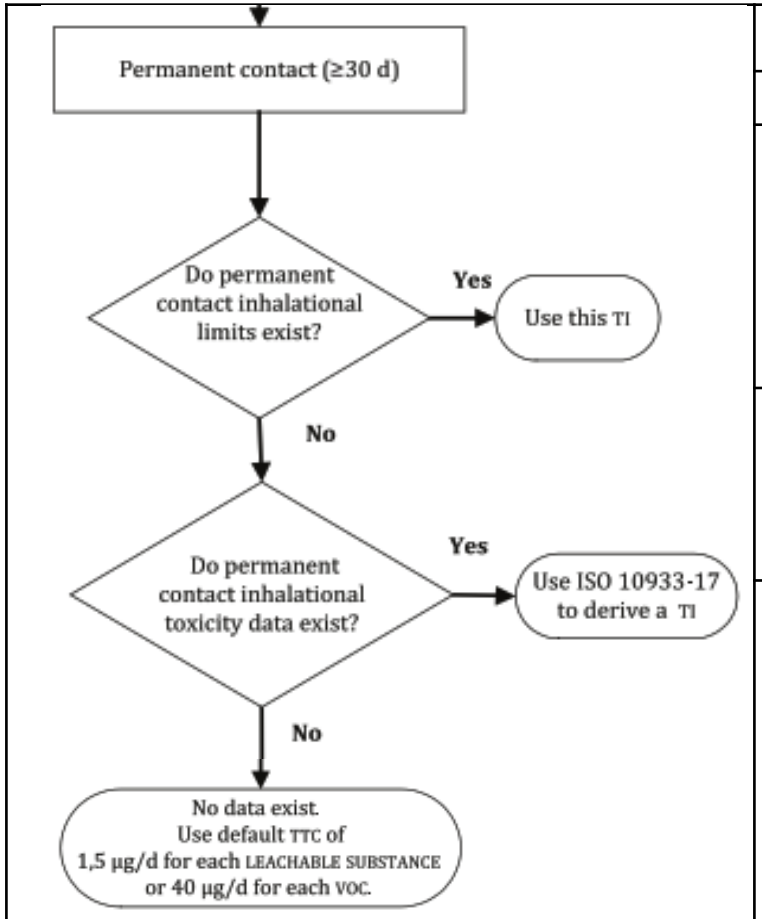


Figure above from: ISO 18562-1, Permanent Exposure Duration Device

Overall Risk Assessment Method used in this Report
- For all VOCs, genotoxicity data was reviewed for any indication of carcinogenicity
Regulatory Limit: when an exposure inhalation limit from internationally accepted toxicological database exists, it was used as the TI. - The point of departure and uncertainty factors used to derive the limit were verified to be adequate; - *The MOS was found by comparing the TI (regulatory limit) directly to the measured concentration.*
Toxicity Data: when no regulatory limit exists, toxicity-based data from an alternate reliable source were modified using uncertainty factors and methods described in ISO 10993-17 to calculate the TI. - TI was converted to a TE using patient body weight, and methods described in ISO-18562-1; - *The MOS was found by comparing the TE directly to the patient daily exposure*
TTC for VOCs: when the no regulatory limit or toxicity data exists, the VOC TTC for the appropriate exposure period, presented in the ISO-18562 guidelines, was adjusted for patient body weight and used as the TI. - TTC can be adjusted for patient population or converted to a concentration using patient DIV, and methods described in ISO-18562-1; - *The MOS was found by comparing the patient population TTC to the patient daily exposure or the TTC concentration directly to the measured concentration.*

Some Notes…

Regulatory Limit:

- Check to see if values were derived with consideration of carcinogenic endpoints (ex: Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRL) do not)
- Check that uncertainty factors were selected properly (including patient population)
- Note - some occupational limits are *not* based on toxicity data

Some More Notes…

Toxicity Data:

This allowable limit, or Tolerable Intake (TI), can be adjusted using the patient's body weight to arrive at the Tolerable Exposure (TE) limits (in µg/day).

$$\text{TE limit}\left(\frac{\mu g}{\text{day}}\right) = TI\left(\frac{\mu g}{kg}\right) \times patient\ body\ weight\ (kg)$$

From here, the TE can be divided by the patient's daily inhalation volume to arrive at the permitted concentration (µg/m^3) for the particular patient population when the exposure is continuous.

$$\text{Permitted Concentration}\left(\frac{\mu g}{m^3}\right) = \frac{TI\left(\frac{\mu g}{kg}\right) \times patient\ body\ weight\ (kg)}{patient\ daily\ inhalation\ volume\left(\frac{m^3}{day}\right)}$$

…More Notes…

TTC for VOCs: described in ISO 18562-1 and ISO 18562-3 (for a 70 kg adult).

ISO-18562-1, Clause 7- Deriving Allowable Limits

> Taking a practical approach, the committee discussed the levels at which it was currently possible to measure concentrations using established, standardized laboratory techniques. The current detection limit for vocs using standardized test methods is 2 µg/m^3. Thus, a proposed limit of 2 µg/m^3 as a concentration is as low as possible to measure. A concentration of 2 µg/m^3 gives a total dose-to-PATIENT for an adult (who breathes 20 m^3/d) of 40 µg. Thus, if any TTC limit below 40 µg/d were to be proposed, it would be meaningless, as it would not be possible to measure it.

Table 1 — TTC limits by exposure

Exposure category	Length of PATIENT exposure	TTC ug/d		
Limited exposure	≤24 h	360	—	—
Prolonged exposure	>24 h and <30 d	360, for first 24 h	120, for the subsequent 29 d	—
Permanent contact[a]	≥30 d	360, for first 24 h	120, for the subsequent 29 d	40, beyond 30 d

[a] Figure 1, green bar E or blue curve G.

More Notes…

Use the PROCESS described in 6.2 (adjustment for body weight) to convert the TOLERABLE INTAKE (in µg/kg body weight/d) into a TOLERABLE EXPOSURE (in µg/d). This PROCESS results in identifying an allowed dose-to-PATIENT, in µg/d, of this substance.

The equation below converts that value to a TTC limit for a 0.5 kg neonate:

$$\text{TTC for neonate} = \frac{\text{TTC for adult} \times \text{neonate body mass}}{\text{Adult body mass}}$$

Exposure period	TTC (70 kg)	TTC (0.5 kg)
< 24 hours	360 µg/day	25.7 µg/day
> 24 hours to < 30 days	120 µg/day	8.6 µg/day
> 30 days	40 µg/day	2.9 µg/day
Note these exposure periods in comparison to VOC sampling time points. If your last sample point is at 7 days (168 hrs), you must assume that measured level stays constant indefinitely So, for a compound without a regulatory limit or available toxicity data measured at 80 ug/day at 168 hrs, the TTC will be acceptable if device use is 29 days or less BUT will not be acceptable if device use is permanent Some labs calculate a TWA using sample concentrations/ time points.		

18562-4: Leachables in Condensate

5.4 LEACHABLE SUBSTANCES in condensate

If condensation can occur in the MEDICAL DEVICE and this condensate can reach the PATIENT, evaluation shall be performed for the presence of harmful LEACHABLE SUBSTANCES according to ISO 18562-4. Only sections of the GAS PATHWAY from which the PATIENT can be exposed to condensate need be tested. If the MEDICAL DEVICE under evaluation has already been evaluated as tissue contacting according to ISO 10993-1, then LEACHABLE SUBSTANCES tests need not be performed in addition.

(Dare I say) FDA's expectations are closer to ISO 10993-18 (2020) than to 18562-4 (2017)

- Extraction at 50 °C for 72 hr, minimum
- Use of polar, non-polar, semi-polar solvents (Consider feasibility or compatibility testing of solvents)
- Semi-volatile, non-volatile, & elemental compounds (i.e., GC/MS, LC/MS, ICP/MS)
- Must use an appropriate AET limit
- Not accepted: "1 mL solvent volume" adjustment to estimate exposure! (See CDRH recognized consensus standards)
- Only surfaces that are in contact with gases or liquids that can be inspired are relevant. This can help when it comes to meeting the AET, also consider filling a component instead of submerging for the extraction.

REALLY need to have a lab that knows what they are doing.

The End.

Thank you!