ISO 18562 Series
Biocompatibility evaluation of breathing gas pathways in healthcare applications

Medical Device and Combination Product Specialty Section

SOT | Society of Toxicology
Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

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LIVE WEBINAR
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James (Morrison) has 30 years experience in product development. The last 13 years in medical devices, particularly for Respiratory Medicine.

Expertise materials for respiratory devices and device validation, including biocompatibility. Materials Science and Toxicology background.

A member of ISO/TC 194 (Biocompatibility, ISO 10993) for some years and current Head of the Australian delegation.

Was very active in the development of the ISO 18562 series through ISO/TC 194 Task Force in liaison with ISO/TC 121 (Lung Ventilation)

Currently heavily engaged in ISO 10993 Part 17 & Part 18 revisions.

Brandwood Biomedical is a Sydney, Australia based consultancy to the global medical device industry.
Biocompatibility evaluation of breathing gas pathways in healthcare applications –

• Part 1: Evaluation and testing within a risk management process
• Part 2: Tests for emissions for particulate matter
• Part 3: Tests or emissions of volatile organic compounds [VOCs]
• Part 4: Tests for leachables in condensate

ISO 18562:2017
Gas pathway medical devices are ubiquitous

Limited standardisation: equipment or air

Contact durations: Transient, Limited – Long term

Single use – Multiple uses/multiple users (years)

Device derived substances (not environmentals)

Particles, vapours & leachables

$\text{CO}_2$, CO, $\text{O}_3$ possible future parts
Part 1 “Evaluation & Testing”

Covering document

ISO 10993 doesn’t really cover gas pathways

Type tests

Duration of use

Flowchart to determine testing required

Toxicological considerations introduced

Body weights

Breathing volumes
Part 1 (cont.)

Allowable limits

Deriving tolerable intakes

Thresholds of Toxicological Concern (in the absence of tox data)

- \( \leq 24 \text{ h} \) \( \rightarrow \) 360 \( \mu \text{g/d} \)
- \( > 24 \text{ h}, < 30 \text{ d} \) \( \rightarrow \) 120 \( \mu \text{g/d} \)
- \( > 30 \text{ d} \) \( \rightarrow \) 40 \( \mu \text{g/d} \) (VOCs)
- 1.5 \( \mu \text{g/d} \) (Leachables in condensate)*

* Note the ICH M7 correlation
Part 2 Particulates

Particle diameters 0.2 – 10 µm

PM$_{2.5} < 12$ µg/m$^3$

PM$_{10} < 150$ µg/m$^3$

Independent of particle chemistry/material
Part 2 Tests

- Largely based on historical environmental air quality monitoring methods (filter mass balance, etc)
- These may be difficult to apply to medical devices
- Particle counters are acceptable (with calibration!)
- Use worst case conditions
- Understand particle source/origin & causes
- Consider “time varying emissions”
Part 3 Volatile Organic Substances

50°C < T_b < 250°C

Toxicological Risk Assessment

- Dose to patient
- Tox data available
- Dose < TI

No tox data → TTC
Part 3 (cont.)

TTCs by exposure duration

Table AND Graph

Table 1 — TTC limits by exposure

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Length of patient exposure</th>
<th>TTC ug/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited exposure</td>
<td>≤24 h</td>
<td>360</td>
</tr>
<tr>
<td>Prolonged exposure</td>
<td>&gt;24 h and ≤30 d</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>for first 24 h</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>for subsequent 29 d</td>
<td></td>
</tr>
<tr>
<td>Permanent contact a</td>
<td>≥30 d</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>for first 24 h</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>for subsequent 29 d</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>beyond 30 d</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. green bar E or blue curve G.
Part 3 Tests

Largely based on historical environmental air quality monitoring methods (steel chamber/traps, etc)

These may be difficult to apply to medical devices

Absorption tubes acceptable (e.g. Tennax, activated charcoal & specifics)

Use worst case conditions

Understand particle source/origin & causes

Consider “time varying emissions”
Time varying emissions would conform to diffusion models (e.g. Arrhenius)

Exponential power curves – (min 4 points)
Part 4 Leachables in Condensate

“quantify hazardous water-soluble substances that are leached ... by condensate and then conveyed by that liquid to the patient”

Dose determinations may (very likely) be contentious.

Three conditions must be met:

• Gas in the gas pathway can reach 100% saturation with water at some point in the gas pathway
• Condensate can form on the gas pathway surfaces
• Liquid condensate can reach the patient
Part 4 Tests

- Leachables study, to make an extract
- Instrumented analysis for organics & metals. (e.g. GC/MS & ICP/MS)
- Identify VOCs & SVOCs
- Toxicological Risk Assessment
- Can use exhaustive extraction, but might be unnecessarily expensive
- Environmental contaminants laboratories
- WILL need some biological tests
<table>
<thead>
<tr>
<th>Types of Analytes</th>
<th>Types of Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive ID, with tox data</td>
<td>Calculate TI</td>
</tr>
<tr>
<td>Positive ID, with no tox data</td>
<td>QSAR, Read across, etc <strong>OR</strong> TTC</td>
</tr>
<tr>
<td>Tentative ID, with tox data</td>
<td>QSAR, Read across <strong>AND</strong> Calc TI</td>
</tr>
<tr>
<td>Tentative ID, with no tox data</td>
<td>TTC</td>
</tr>
<tr>
<td>Unknown ID, with structural data</td>
<td>QSAR, Read across, etc <strong>AND</strong> TTC</td>
</tr>
<tr>
<td>Unknown ID, with no structural data</td>
<td>TTC</td>
</tr>
</tbody>
</table>
Time for Q&A...

Think of something later? Ask us by email...
James@brandwoodbiomedical.com
Big THANK YOU to: SOT

& participants and interested parties in this webinar.