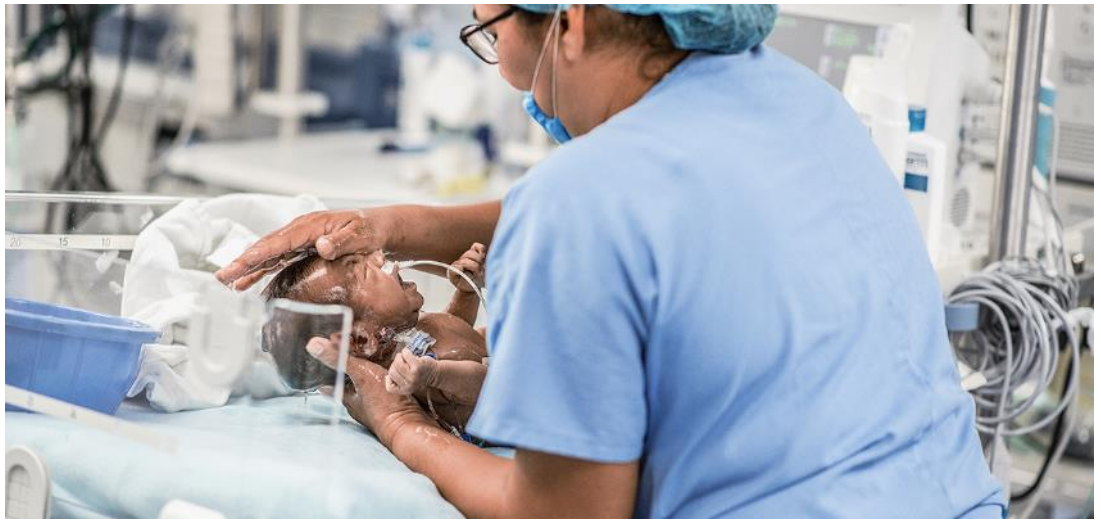
New Biocompatibility Requirements for Medical Devices

Anke van Stevendaal
April 2024, Burghausen

Content

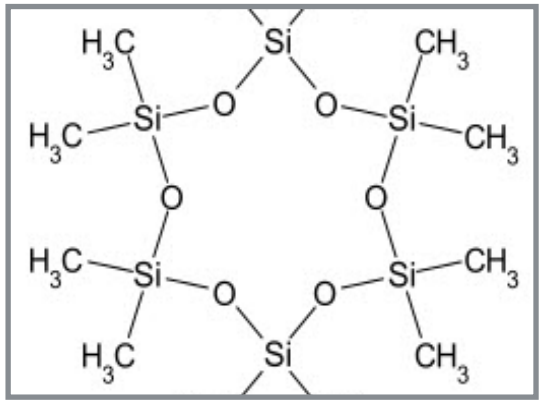


Chapter 01

Short introduction of Dräger
Usage of Silicones

Chapter 02

Toxicity of Siloxanes



Chapter 03

New Substance topic: Cohorts of concern (CoC); Material mediated pyrogenicity

Chapter 04

Biocompatibility over expected life time

01

Introduction Dräger Usage of Silicones

Dräger
in profile

Employees:
16.219

Chairman of the Executive Board:
Stefan Dräger
family-run

Form of business organization:
AG & Co. KGaA

Sales and service:
~50 countries

Figures from fiscal year 2022

Net sales:
3 bn. €

Headquarters:
Lübeck
Germany

Production sites
Germany, Chile, China, France, U.K., India, Sweden, South Africa, Czech Republic, U.S., Norway, Switzerland, Lithuania, Serbia

Technology for Life

Dräger


We are there
when life begins.


We support medical professionals worldwide in protecting, supporting, and saving lives.


We help save the people
who save lives.


We help keep
air breathable,
even underground.

Applications for Silicones at Dräger

Medical Equipment

Neonatology

Pediatrics

Gas Management Systems

Intensive Care

Anesthesia Devices

Applications for Silicones at Dräger

Examples for molded parts made of HCR

Examples: parts out of the breathing system
standard HCR,
addition cure types and
self-adhesive types

Applications for Silicones at Dräger

Examples for extruded parts made of HCR

Examples:
Hoses and Profiles
made of standard HCR,

02

Toxicity of Siloxanes

ISO 10993

Biological Evaluation of Medical Devices

This standard describes how to assess, whether a medial device might have a negative impact to the patient. Part 1 to part 23 of this standard addresses for example the following topics:

- **It is determined which tests must be carried out depending on the kind of patient contact (implant, contact to skin - healthy or wounded, contact to a mucous membrane, contact to breathing gas, ...)**
- **The different tests are described (test for cytotoxicity, animal related tests like sensitization, irritation, carcinogenicity, ...)**
- **It is specified how to determine/apply limit values for the different scenarios**
- **Assessing the biocompatibility in the scope of a risk management procedure is given in a flow chart**
- **...**

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Just a mark is embedded to jump to....

ISO 18562

Biocompatibility Evaluation of Breathing Gas Pathways in Health Applications

Currently valid edition from 2017

New edition was published in March 2024.
Valid dates depend on the different countries, and the different transition periods

Part 1: Evaluation and testing within a risk management process

Part 2: Tests for emissions of particulate matter

Part 3: Tests for emissions of volatile organic compounds (VOCs)

Part 4: Tests for leachable in condensate

ISO 18562-3

Emissions of VOCs from Silicones – Siloxanes

In the case of silicone parts, the most important „VOCs“ are the siloxanes, or more specifically cyclic volatile methyl siloxanes (cVMS).

Trivial name	Chemical name	Compliance remarks
D3	Hexamethylcyclotrisiloxane	
D4	Octamethylcyclotetrasiloxane	SVHC
D5	Decamethylcyclopentasiloxane	SVHC
D6	Dodecamethylcyclohexasiloxane	SVHC
D7	Tetradecamethylcycloheptasiloxane	
…		
D12 (already found in Dräger analysis)		

VOC = Substances with a boiling temperature of 50 to 260 °C (i.e. D7 is already semi-volatile)

ISO 18562-3

Definitions of Toxicological Terms

Definition TI = Tolerable Intake

Amount of a specific substance in µg/kg body weight per day to which a patient can be exposed that is considered to be without appreciable harm to health.

Definition TE = Tolerable Exposure

Amount of a substance, in µg/day to which a patient can be exposed to that is considered to be without appreciable harm to health (already scaled according to patient body weight).

Definition TTC = Toxicological Threshold of Concern

Level for all substances in µg/day that poses no appreciable risk to human health, regardless of whether the identity of the substance is known or not.

Patient group	Default body weight	Default air intake (resting)
Premature neonates	0.5 kg	0.26 m^3/day
Infants	3.5 kg	2.3 m^3/day
Small Children	10 kg	5.1 m^3/day
Children	20 kg	6.0 m^3/day
Adolescents	32 kg	7.7 m^3/day
Adults	60 kg	11.5 m^3/day

New according to ISO 18562-1:2024

ISO 18562-3

Toxicological Limits for cVMS – Siloxanes

Tolerable exposure concentration in µg/m³ in the breathing gas.

Example: long-term contact (> 30 days, relevant for a ventilation in intensive care)

Trivial name	Chemical name	Limit for adults	Limit for infants
D3	Hexamethylcyclotrisiloxane	9900	4950
D4	Octamethylcyclotetrasiloxane	26400	13190
D5	Decamethylcyclopentasiloxane	8700	4350
D6	Dodecamethylcyclohexasiloxane	200	90
D7	Tetradecamethylcycloheptasiloxane		
…			
D12 (already found in Dräger analysis)			

ISO 18562-3

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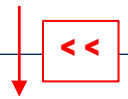
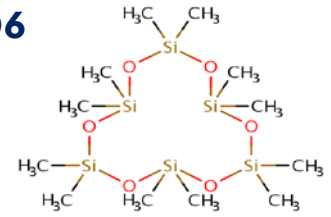


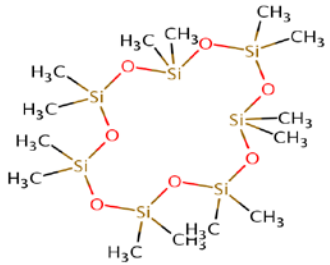
?

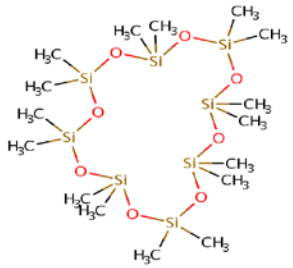
ISO 18562-1 and -3

Toxicological Risk Assessment for cVMS

- D3, D4, D5: high limit values → passed result
- D6: low limit values → failed result
- D7, D8, D9, etc.: no toxicological data are available. Because of the similarity of the molecules D6 is used to estimate corresponding limit values (“read-across approach”)
  low limit values → failed results.

D6 

D7 

D8 

- Unspecified siloxanes: The very low TTC value must be used → failed result.

ISO 18562-3

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...			
D12			

ISO 18562-3

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D7	Tetradecamethylcycloheptasiloxane		35
D8	Hexadecamethylcyclooctasiloxane		40
…			…
D12			60

<< <<

Read-across approach

ISO 18562-3

Examples of Test Results

Example: Breathing machine with many different raw materials and silicone parts, post cured (4h/200°C)

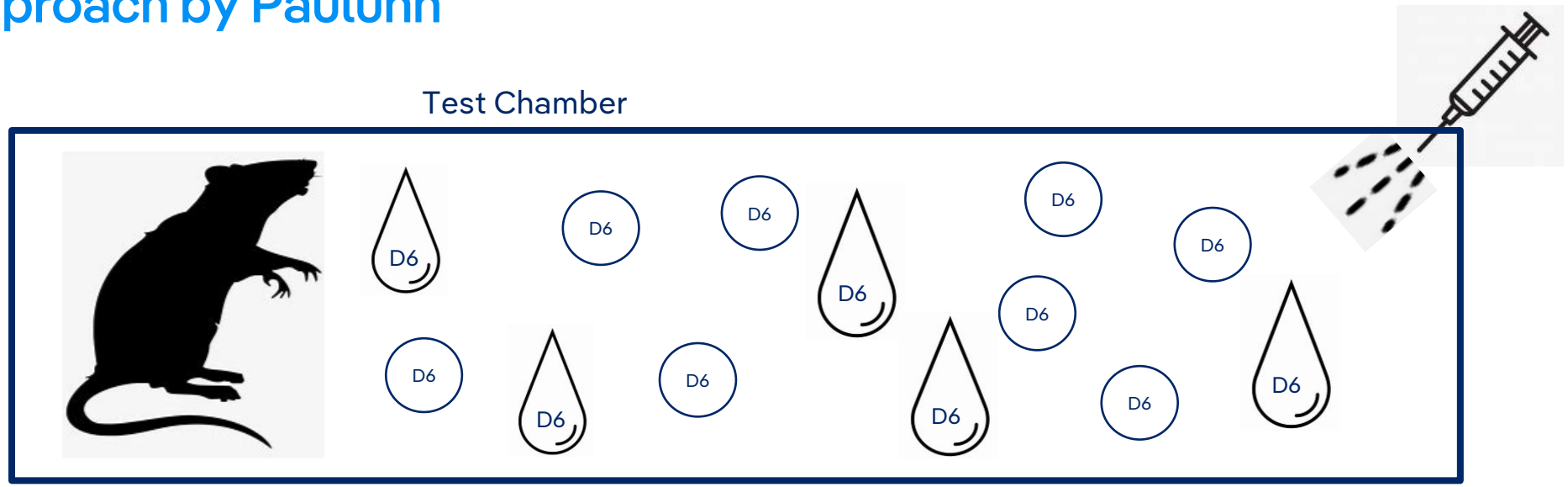
Stoffgruppe	Stoff	Ergebnis µg/m³	BG µg/m³	CAS
Siloxan	Octamethylcyclotetrasiloxan	8	2	556-67-2
Siloxan	Siloxan	2	2	
Siloxan	Siloxan	11	2	
Siloxan	Decamethylcyclopentasiloxan	82	2	541-02-6
Siloxan	Dodecamethylcyclohexasiloxan	104	2	540-97-6
Siloxan	Siloxan	3	2	
Siloxan	Tetradecamethylcycloheptasiloxan	64	2	107-50-6

ISO 18562-1 and -3

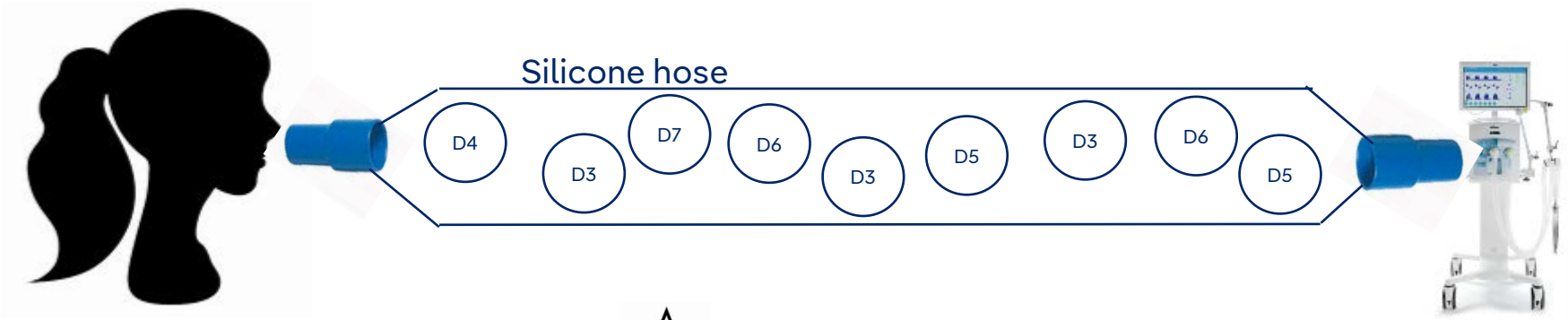
New Approach by Pauluhn

Test Scenario

Test Chamber



Real Application



D4 = single molecule

D6 = aerosol particle

ISO 18562-1 and -3

New Approach by Pauluhn

A new perspective on cVMS inhalation toxicity:

The adverse effects of D6 inhalation exposure are related to the formation of liquid aerosol particles (therefore phase-specific), which can disturb the surfactant system within the lung.

Saturation pressure is typically not exceeded in human exposure scenarios as silicone compounds only passively emit small amounts of cVMS.

Pauluhn proposed an assessment approach, which focusses on keeping the tolerable exposure concentration below saturation pressure.

→ "V_{sat} approach"

ISO 18562-1 / 18562-3

Regulatory Acceptance of the V_{sat} Approach

Why not just use the V_{sat} approach?

- **The V_{sat} approach is no a standard procedure.**
- **The EU LCI group (LCI = “lowest concentration of interest”) uses of the V_{sat} approach. This a first step towards international acceptance.**
- **LCI values are still less popular compared to other limit values (e. g. RfCs, MRLs, etc.)**
- **LCI values are derived for emissions from construction products but also relevant for assessing inhalation risks (e.g. associated with medical devices).**

It might be helpful to request ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) to evaluate the “V_{sat} approach” for chemicals like the siloxanes D6, D7, D8 ff (showing toxicity based on their physicochemical properties) and in the best case create further acceptance.
(Wacker seems to be a member of the organization)

03

Cohorts of Concern (CoC)
Material mediated pyrogenicity

Cohorts of Concern (CoC)

ISO 18562 – 4 and ISO 10993 – 17

ISO 18562- 4 Tests for leachable substances in condensates
ISO 10993-17 Toxicological risk assessment for components of medical devices

The following substance groups belong to the CoCs:

Aflatoxin-like compounds
N-Nitroso compounds
Azo compounds
Polyhalogenated -dibenzodioxins, -dibenzofurans, and -biphenyls
Strained heteronuclear rings
Heavy metals (e.g. elemental, ionic, or compounds)
Alpha-nitro furyl compounds
Hydrazines/triazenes/azides/azoxy compounds
Polycyclic amines
Steroids
Organophosphorous compounds

Material mediated pyrogenicity (Entzündungen hervorrufende Stoffe)

ISO 10993-11

ISO 10993-11 Tests for systemic toxicity (also to assess in the watery extract)

The following substance groups are in the focus:

Endogenous Pyrogens (e. g. IL-1, IL-6, TNFα, INF-γ)
Prostaglandin
Inducers (e. g. Polyadenyl-, Polyuridyl-, Polybionosin- and Polyribocytidyl acid)
Substances that interrupt the function of the thermoregulation centers(e. g. LSD, Cocain, Morphin)
Substances that uncouple oxidative phosphorylations (e. g. 4, 6-Dinitro-o-Kresol, Dinitrophenole, Picric acid)
N-Phenyl-β-naphthylamine and Aldo-α-naphthylamine (the fever-inducing mechanism is unknown)
bacterial Exotoxins (e. g. TSST-1, SEA, Spe F, Spe C)
Neurotransmitters (e. g. Noradrenaline, Serotonin)
in some cases, metals such as nickel salts

Material mediated pyrogenicity and CoC

How to deal with these new requirements?

The above-mentioned standards request a special treatment for the substance groups:

„Cohorts of Concern“. These substances are that toxic that no threshold value (TTC) does exist.

Substances that can cause a “material mediated pyrogenicity” should be avoided completely.

How to ensure, that these substances are not contained in our products?

Analytical methods would require very detection limits for many substances → very difficult!

Normative approach:

→ Asking the suppliers with knowledge about ingredients and processes.
→ Avoid animal tests!

04

Biocompatibility over expected Lifetime

Biocompatibility over expected lifetime …

… and expected service life (that can be longer than the exposure period) is required by

ISO 10993-1:2018

ISO 18562-1:2024 → raw materials in the gas pathway are directly within the scope

Effect on the approval tests for Dräger Devices:

An assessment must be given for all raw materials in contact to breathing gas after approx. 15 years usage. More than 50 different polymeric materials are in use in devices like Breathing Machines or Anesthesia Machine.

Task:

Think about a test routine that simulates the “real life” of a Medical Device.

Biocompatibility over expected lifetime

The Standard tells us to consider the following aspects?

Effects of **storing** during **shelf life**

Effects of operation during **intended use**

Potentially harmful substances are added to the raw material matrix by migration

Ware

Reprocessing: cleaning, disinfection, sterilization

Handling

Environmental Impact
Temperature, humidity, pressure, sunlight, UV light

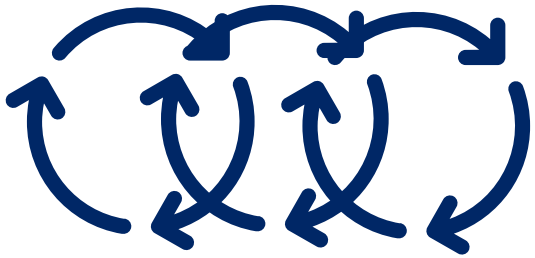
Biocompatibility over expected lifetime

For example: What does that mean translated to an anesthesia machine?

Effects of storing
Accelerating aging tests in normal air

Effects of
contact to the 3 liquid aesthetic agents

Mechanical ware for dynamically used parts



Potentially harmful
- Medicines are applied by a nebulizer
- Device is parked in a room with “bad” air

cle
- Emerge the relevant materials in disinfectants
- Carry out thermal and humid disinfection cycles

Opening and closing the breathing system for reprocessing

Environmental Impact
Contact to oxygen, to laughing gas and to other medical gases

Take Home Message

A

Toxicology

Request ECETOC to assess the **“V_{sat} approach”.**

B

Substance requirements

Be warned, that customers might ask you concerning CoC and material mediated pyrogenicity.

C

Evaluation over lifetime

Ideas, how to simulate the lifetime of a medical devices are always welcome.

Time for questions

Thank you

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