Evaluation

Sponsor	PROCON Gesellschaft für Kontinenzversorgung und Rehabilitation mbH, Dr. A. Heimerl, Saseler Bogen 6, D-22393 Hamburg
Date of order	06-10-26/06-11-07
Evaluation	Biological safety - toxicology (EN ISO 10993-1, Directive 93/42/EEC)
Documentation	Presented by the sponsor
Expert	Dr. Stephan Rossberger
Note	This evaluation refers only to the documentation presented by the sponsor. Confidential - for exclusive use of the sponsor and registration authorities.

Product/material	Enutrain sensor (R4502) [4].
Manufacturer	Procon GmbH
Intended use	Bedwetting therapy for children, single patient, multiple use [4].
Body contact	Indirect contact to skin (perspiration-mediated, the sensor is placed in an adhesive sanitary towel within the underwear) up to 12 h per day (< 24 h), repeated use, only inadvertant direct and/or urine-mediated prolonged indirect skin contact [4].
Surface area	< 40 cm^2
EN ISO 10993-1	Biological effects to be considered are cytotoxicity, tissue irritation, sensitization.
Sterilization method	- (not applicable)
Remarks	This evaluation refers only to toxicologically relevant effects of potential leachable substances from the tested materials. Potential mechanically induced skin irritations and /or interactions of the materials with cleaning or disinfectant solutions are not within the scope of this assessment.

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Test matrix

Toxicological tests performed on the device

Material	Test	Ref.	Comments	Result
Enutrain sensor R4502	Cytotoxicity ISO 10993-5	[1]	4,5 cm²/ml /DMEM-FBS 24 h, 37 °C	n.n.
	Chemical analysis ISO 10993-18	[2]	3 cm²/ml ethanol/water (1:20), 24 h, 37 °C, GC-FID quantitative determination of organic leachables	n.n. < 1 µg/cm²/24 h
		[2]	3 cm²/ml isopropanol, 24 h, 37 °C, GC-MS characterization of organic extractables	characterized
		[3]	3.8 cm²/ml dest. water, 24 h, 37 °C, ICP-OES for heavy metals (Pb, Cd, Cr, Ni, Cu, Zn, Hg), AAS for silver	n.n. (≤ 5 ng/cm²/24 h)

n.n. = no toxicologically relevant effects observed in comparison to the controls

Evaluation

The Enutrain sensor (R4502) does not affect the biological safety of the patient/user by leachables for the following reasons:

- Extracts of the device components have been tested in a cell culture test system, which allows a very sensitive characterization of the resting „solubility" of materials (organic and anorganic leachable residues and contaminants). The test and extraction method has been specifically designed to ensure most sensitive detection of toxic leachables on cellular level (e.g. more than 2-fold more sensitive than USP elution method). No cytotoxic effects were obtained in presence of the extracts.

- The results of highly sensitive chemical analyses (gas chromatography, GC-FID) performed with aqueous/ethanolic extracts confirm the inert properties of the materials. The total amount of organic leachables was below the detection li-

mit of 1 µg/cm²/24 h under simulated use conditions. Therefore, the residues detected in solvent extracts prepared under material-destructive conditions (isopropanol, 24 h, 37 °C) will not be released in toxicological relevant concentrations during application of the device. As well, no toxic heavy metals or leachable silver have been obtained in aqueous extracts.

- The occasional, indirect, and surface-limited contact to skin negates the release of substances in concentrations persistently hazardous to the patient/user.

No skin irritation or sensitization testing were performed on the device component. This is justified because of the inert material properties proven by highly sensitive biological and chemical test methods. Extraction conditions and test methods used exceed actual normative requirements to provide highest possible safety levels for the patients. From the results obtained, it can be stated that extracts prepared by standard procedures (compatible with biological test systems) will not contain substances in toxicologically relevant concentrations and/or concentrations high enough to elucidate any responses in biological test systems. Therefore, there is no adequate sensitivity and no need of further testing.

The insolubility of the Enutrain sensor (R4502) is in compliance with ISO 10993-1 for the intended use. There is no evidence that hazardous effects to the patient/user will arise by leachable ingredients and/or residues.

Dr. Stephan Rossberger

Documentation [ ]

1. Medical Device Services: Testbericht 063747-20, Cytotoxizität, Enutrain Sensor (R4502), 2006.
2. Medical Device Services/SAS: Testbericht 063753-30-A, chemische Analyse, Enutrain Sensor (R4502), 2006.
3. Medical Device Services/SAS: Testbericht 063753-30-B, Schwermetallanalyse, Enutrain Sensor (R4502), 2006.
4. Procon: Correspondence, specification of the device and materials, 2006.