Date: 21.04.2021

Field Safety Notice
EXHALYZER D

For Attention of*: Identify either by name or role who needs to be aware of the hazard and/or take action. If this is multiple recipients then include full list.

Contact details of local representative
Acertys Healthcare nv, Oeyvaersbosch 12, BE-2630 Aartselaar, Tel: +32 3 870 11 11, www.acertys.com
MATREL d.o.o., Baštijanova 9a, HR-10 000 Zagreb, Tel: +385 1 3633 055, www.matrel.hr
TECHNOPROCUR CZ, spol. s r.o., Lipova 524, 252 43 Pruhonice, Tel: +420 241 716 024, www.technoprocur.cz
Intramedic A/S, Gentoftegade 118, 2. Sal, 2820 Gentofte, Tel: +45 7023 6162, www.intramedic.dk
Timik Medical Oy, Innopark 2, Vankanlähde 7, 13100 Hämeenlinna, Tel: +358 757 580 860, www.timik.fi
Adhesia Division Diagnostics, 26, Rue de la montée, 68820 Flaxlanden, Tel : +33 3 89 06 14 44, www.adhesia.com
ECO PHYSICS GmbH, Gildenweg 6, D-50354 Hürth, Tel: +49 2233 46055 00, www.ecophysics.de
ANNOX Ltd., 3 Cowper Crescent, Hertford, Herts, SG14 3DY, Tel: +44 1 992 534 643, www.annox.co.uk
Analytical Instruments S.A., 9, Tzavella str., 152 31 K. Chalandri/Athens, Tel: +30 210 67 48 973, www.analytical.gr
Med-Pro Hungary kft., Perényi út 8/b, 1037 Budapest, Tel: +36 1 250 1463, www.med-pro.hu
Sormedica Co. Ltd, Kuzmos str. 28, 08431 Vilnius, Tel: +370 (5) 219 57 10, www.sormedica.lt
Medical Graphics Italia Srl, Via Simone d'Orsenigo, 21, 20135 Milano, Tel: +39 02 54 12 03 43, www.medgraphics.it
AkuMed A.S., Østensjøveien 27, Postboks 6253, Etterstad, 0603 Oslo, Tel: +47 22 07 52 20, www.akumed.no
PRO VITA Polska Sp. z o.o. Sp.K., Ul. Parafialna 1, 47-100 Strzelce Opolskie, Tel: +48 77 462 13 00, www.sprzetmedyczny.pl
PULMOCOR, Rua José Joaquim de Freitas, 253, PO Box 46, 2751-901 Cascals, Tel: +35 1 214 841 840, www.pulmocor.pt
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SANRO Electromedicina S.A., Ctra. de Húmera 10, 28224 Pozuelo de Alarcón (Madrid), Tel: +34 (91) 352 92 44, www.sanro.com
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Eldan Electronic Instruments Co.Ltd., 6 Hashiloach Street, Petach-Tikva 49170, Tel: +972 3 9371144, www.eldan.biz
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TEKNIKEL Ticaret ve Sanayi A.S., Piyalepasa Bulvari, Kastel Is Merkezi, C-Blok Kasimpasa, Istanbul, Tel: +90 212 254 7400, www.teknikel.com

Field Safety Notice (FSN)
EXHALYZER D

	1. **Information on Affected Devices***
1.	1. Device Type(s)*
	EXHALYZER D
1.	2. Commercial name(s)
	-
1.	3. Unique Device Identifier(s) (UDI-DI)
	-
1.	4. Primary clinical purpose of device(s)*
	Pulmonary Function Testing Device
1.	5. Device Model/Catalogue/part number(s)*
	M3024 with option M3024-12 (N2-MBW)
1.	6. Software version
	Spiroware 3.3.0 or previous versions
1.	7. Affected serial or lot number range
	All
1.	8. Associated devices
	None

	2. **Reason for Field Safety Corrective Action (FSCA)***
2.	1. Description of the product problem*
	O2 and CO2 Sensor cross sensitivity
2.	2. Hazard giving rise to the FSCA*
	None, when correct normative values are used.
2.	3. Probability of problem arising
	All FRC / LCI measurements might be affected
2.	4. Predicted risk to patient/users
	No risk for patient or user
2.	5. Further information to help characterise the problem
	Using correct normative values does not lead to any misinterpretation of clinical outcome.
2.	6. Background on Issue
	Scientific publications as listed in the attached report summary.
2.	7. Other information relevant to FSCA
	-

	3. Type of Action to mitigate the risk*	
3.	**1. Action To Be Taken by the User***	
	☐ Identify Device ☐ Quarantine Device ☐ Return Device ☐ Destroy Device ☐ On-site device modification/inspection ☐ Follow patient management recommendations ☐ Take note of amendment/reinforcement of Instructions For Use (IFU) ☒ Other: Software update by customer as soon as possible, latest at the next yearly maintenance or at the end of clinical trial ☐ None Provide further details of the action(s) identified.	
3.	2. By when should the action be completed?	As soon as possible, latest at the next yearly maintenance or at the end of clinical trial
3.	3. Particular considerations for: Diagnostic Imaging device Is follow-up of patients or review of patients' previous results recommended? No -	
3.	4. Is customer Reply Required? * (If yes, form attached specifying deadline for return)	Yes 31.05.2021
3.	**5. Action Being Taken by the Manufacturer** ☐ Product Removal ☐ On-site device modification/inspection ☒ Software upgrade ☐ IFU or labelling change ☐ Other ☐ None **Software update available for download**	
3	6. By when should the action be completed?	As soon as possible, latest at the next yearly maintenance or at the end of clinical trial
3.	7. Is the FSN required to be communicated to the patient /lay user?	Yes
3	8. If yes, has manufacturer provided additional information suitable for the patient/lay user in a patient/lay or non-professional user information letter/sheet? Yes Appended to this FSN	

	4. General Information*	
4.	1. FSN Type*	New
4.	2. For updated FSN, reference number and date of previous FSN	-
4.	**3.** For Updated FSN, key new information as follows:	
	-	
4.	4. Further advice or information already expected in follow-up FSN? *	No
4	5. If follow-up FSN expected, what is the further advice expected to relate to:	
	-	
4	6. Anticipated timescale for follow-up FSN	31.05.2021
4.	7. Manufacturer information (For contact details of local representative refer to page 1 of this FSN)	
	a. Company Name	**ECO PHYSICS AG**
	b. Address	**CH-8635 Duernten**
	c. Website address	**www.ecomedics.com**
4.	8. The Competent (Regulatory) Authority of your country has been informed about this communication to customers. Not required, the incident is rated as non-serious incident in accordance to Swiss and European Materiovigilance.	
4.	9. List of attachments/appendices:	**AM21-022-Report_Summary V11**
4.	10. Name/Signature	**Dirk Wendt, CEO / MSO / PRRC**

	Transmission of this Field Safety Notice
	This notice needs to be passed on all those who need to be aware within your organisation or to any organisation where the potentially affected devices have been transferred. (As appropriate) Please transfer this notice to other organisations on which this action has an impact. (As appropriate) Please maintain awareness on this notice and resulting action for an appropriate period to ensure effectiveness of the corrective action. Please report all device-related incidents to the manufacturer, distributor or local representative, and the national Competent Authority if appropriate, as this provides important feedback..*

Note: Fields indicated by * are considered necessary for all FSNs. Others are optional.

Improved Accuracy of N_2 Multiple Breath Washout by Signal Correction of EXHALYZER®D O_2 and CO_2 Sensors

Key findings:

- The magnitude and importance of a previously unknown reciprocal cross-sensitivity of the EXHALYZER®D O_2 and CO_2 sensors has been clarified.
- Key outcomes of the N_2MBW are affected by this cross-sensitivity.
- The cross-sensitivity can be fully corrected applying a newly developed Cross-Talk Correction (XTC) algorithm.
- The XTC algorithm can be applied to existing N_2MBW data for retrospect correction by migration of the N_2MBW database.
- Present data indicates that conclusions made from clinical trials will not change.
- For accurate interpretation of MBW outcomes, normative values generated under the same conditions/same software version must be used.
- The influence on N_2SBW data is not significant.
- An update to SPIROWARE® version 3.3.1 is recommended to benefit from improved accuracy thanks to the XTC algorithm.

Note: In accordance with the Swiss and European materiovigilance the finding of the O_2 and CO_2 cross sensitivity is rated as a non-serious incident.

The EXHALYZER®D is a well-established device for multiple breath washout (MBW), which is used to detect ventilation inhomogeneity and early lung disease. The washout technique uses either the tracer gas nitrogen (N_2) or sulfur hexafluoride (SF_6). The N_2MBW application for the EXHALYZER®D has been introduced in 2012 and is CE MDD approved for clinical use since then. The EXHALYZER®D was validated in a comprehensive study[1]. Furthermore, it convinced in numerous research and clinical studies and shown to be sensitive to therapeutic response when used in clinical trials[2]. More than 400 scientific publications mention the device since 2012.

Driven by several studies describing differences between N_2 and SF_6 MBW tests[3,4,5], we performed an in-depth analysis of the O_2 and CO_2 sensor accuracy together with the lung function research group of the University Children's Hospital Bern[6]. The comparison of the EXHALYZER®D sensors' performance to data obtained from a mass spectrometer revealed a hitherto unknown reciprocal cross-sensitivity of the sensors for O_2 and CO_2 used in the EXHALYZER®D. This cross-sensitivity follows a rather complex, non-linear relationship and leads to overestimation of N_2 concentrations and consequently overestimation of MBW outcomes such as the lung clearance index (LCI) and functional residual capacity (FRC).

In order to correct this cross-sensitivity and improve the EXHALYZER®D's accuracy, we have developed a Cross-Talk Correction (XTC) algorithm, which is implemented in the new SPIROWARE® software version 3.3.1. With the XTC algorithm, the relative N_2 error of the EXHALZER®D for typical concentrations at the end of the washout is better than 3.2%, which is in agreement with the 5% recommendation outlined in the ATS/ERS consensus statement[7].

Implications of the XTC algorithm on N_2MBW data were tested by reloading 1276 N_2MBW A-files of healthy and cystic fibrosis subjects into the new SPIROWARE® 3.3.1. We found a linear relationship between corrected and uncorrected LCI values (Figure 1). The average change in LCI is lower for smaller

LCI, but larger for higher LCI values as found in patients with lung disease. The change of other key parameters was also analyzed. On average, the correction algorithm reduces FRC by 8%. It also reduces the length of the washout by 33% on average. It is important to note that there is a strong correlation between the original and corrected parameters as depicted in figure 1. This means that the correction algorithm does not change any results significantly in a clinical sense, such that a patient with lung disease would have a result as found for healthy subjects and vice versa. From the data we have on hand, we conclude that statements based on N2MBW results, which have been made in clinical studies, would not be changed if the XTC algorithm had been used. Consequently, we suggest that a reanalysis of data from clinical studies is not required.

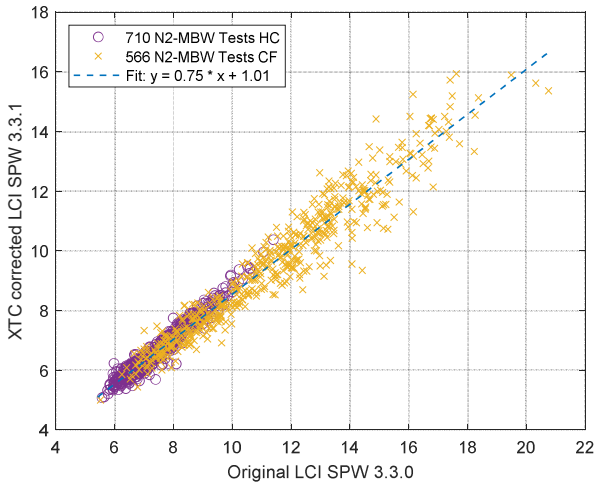

Figure 1: Relationship between corrected and original LCI from 1276 N2MBW tests.

For example, a previous LCI of 8 results in a corrected LCI of 7, while a previous LCI of 16 results in a corrected LCI of 13.

We also investigated the influence of the new XTC algorithm on data from nitrogen single breath washouts(N2SBW). On average, corrected values are slightly smaller than uncorrected values, but there is no significant impact on N2SBW data.

Reference Data

The ATS/ERS consensus statement has noted that normative values always must be generated inert gas and device specific[7]. Data from clinical routine and clinical studies remain valid if the used normative values were generated under the same conditions. Also, if the correction algorithm is applied, our current analysis indicates that clinical conclusions remain unchanged.
For the new SPIROWARE® version 3.3.1, the reference data for N2MBW parameters has been corrected according to the linear relationship described above. This new reference data is unpublished, preliminary data, but can be used for result interpretation until new reference data has been generated and published with the new correction algorithm.

Correction of existing N2MBW data

The retrospect correction of existing N2MBW datasets is possible. In principle, there are two options to correct existing data, migration of the database or reload of A-files.
The easiest and most convenient approach is the migration of the SPIROWARE® database to version 3.3.1 and this approach is recommended for most users. It should be noted that the SPIROWARE® database uses a data compression algorithm applied to the raw data so that small deviations of key parameters can be observed when data is compared to corrected original raw data. For most parameters, the deviation is close to zero.

If small deviations caused by database migration cannot be tolerated, the correction can be achieved by reload of A-files. A-files contain the raw data of a washout trial and this data can be corrected on the individual breath level. However, this approach is more time-consuming.

ECO MEDICS has thoroughly tested both approaches. The fast and simple approach via database migration is recommended wherever possible. Requirements for a successful migration can be found in the release note of SPIROWARE® 3.3.1. We would like to add that an import of spx files has the same effect as a database migration.

How to proceed with N2MBW Data in Clinical Practice

We recommend upgrading to the new SPIROWARE® version 3.3.1 as soon as possible, latest at the next yearly maintenance to benefit from the implemented XTC algorithm. The new version 3.3.1 includes reference data which has been converted in order to be comparable to results obtained with the XTC algorithm. This reference data should be treated as unpublished preliminary data; however, it facilitates the interpretation of results until reference data obtained with the new software version is available.

How to proceed with N2MBW Data in Clinical Trials

In case of clinical trials, it is recommended to complete the trial without changing any measurement and evaluation conditions. If desired, it is possible to correct the complete dataset after conclusion of the trial by automatic database migration or import of patient (spx) files into SPIROWARE® version 3.3.1. At the end of the trial, it is recommended to upgrade to the new SPIROWARE® version 3.3.1.

Nitrogen Single Breath Washouts (N2SBW)

The analysis has shown that the XTC algorithm has a very small impact on the N2SBW results. Although we do not see an urgent need, we recommend upgrading to the new SPIROWARE® version 3.3.1 as soon as possible, latest at the next yearly maintenance to benefit from the implemented XTC algorithm.

Conclusions

The main finding of our investigation was the reciprocal non-linear cross-sensitivity of the O2 and CO2 sensors, which has been fully corrected by an algorithm implemented in SPIROWARE® version 3.3.1. This step presents a great improvement for N2MBW accuracy. Main results of the multiple breath washout are no longer overestimated due to sensor cross-sensitivity and are now in good agreement with results from SF6 washouts both in infants and school children[8]. Apart from more accurate results, another advantage is that the washout time is reduced by one third, which will facilitate, in particular for patients with lung disease, completion of the washout.

References

1. Singer, F., Houltz, B., Latzin, P., Robinson, P. & Gustafsson, P. A realistic validation study of a new nitrogen multiple-breath washout system. PLoS ONE 7, e36083 (2012).
2. Ratjen, F. et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine 5, 557–567 (2017).
3. Yammine, S., Lenherr, N., Nyilas, S., Singer, F. & Latzin, P. Using the same cut-off for sulfur hexafluoride and nitrogen multiple-breath washout may not be appropriate. J Appl Physiol (1985) 119, 1510–1512 (2015).
4. Stahl, M., Joachim, C., Wielpütz, M. O. & Mall, M. A. Comparison of lung clearance index determined by washout of N2 and SF6 in infants and preschool children with cystic fibrosis. Journal of Cystic Fibrosis 18, 399–406 (2019).
5. Bayfield, K. J. et al. Simultaneous sulfur hexafluoride and nitrogen multiple-breath washout (MBW) to examine inherent differences in MBW outcomes. ERJ Open Res 5, (2019).
6. Latzin, P. Pediatric Respiratory Medicine, University Children's Hospital Bern, Switzerland, personal communication.
7. Robinson, P. D. et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. European Respiratory Journal 41, 507–522 (2013).
8. Gustafsson, P. Department of Paediatrics, Central Hospital, Skövde, Sweden, personal communication.