

**Safeguarding Water Quality
HPLC-DAD as Early Warning System**

Meekel, Nienke; de Bar, Marijke W.; Emke, Erik; Pijnappels, Martijn M.; Kooper-Mookerji, Runa; van Diepenbeek, Peter; Fischer, Astrid; van Doorn, René; Asgadaouan, Asmaïl; Bäuerlein, Patrick S.

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Safeguarding Water Quality: HPLC-DAD as Early Warning System

Nienke Meekel, Marijke W. de Bar,  Erik Emke,  Martijn M. Pijnappels, Runa Kooper-Mookerji, Peter van Diepenbeek, Astrid Fischer, René van Doorn, Asmail Asgadaouan, and Patrick S. B auerlein*



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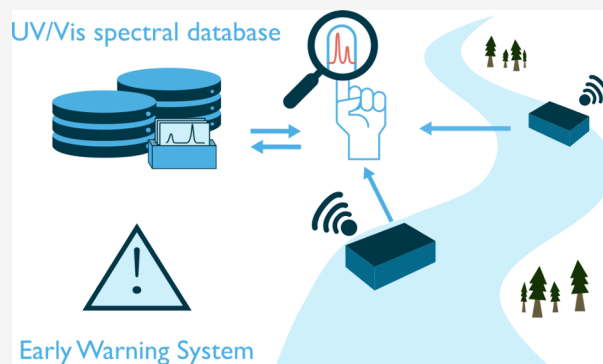


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Supporting Information

ABSTRACT: Harmonized online solid phase extraction (SPE) coupled to high-performance liquid chromatography (HPLC) with diode array detection (DAD) has proven its suitability as a robust early warning system for water quality in The Netherlands. A retention index (KRetI), validated through interlaboratory ring trials, together with a shared UV spectral database, facilitates data comparability across laboratories. The technique enables early detection of trends and incidental contamination, triggering alarm systems, and allowing for measures to be taken to protect the drinking water supply and the river's ecosystem.



INTRODUCTION

The largest part (60%) of high-quality drinking water in The Netherlands is obtained from groundwater, while the remaining 40% comes from surface water sources.¹ This latter source requires substantial treatment efforts due to contamination from anthropogenic chemicals. The main surface water sources of Dutch drinking water are the River Rhine, River Meuse, and Lake IJssel which is fed by the River IJssel, a tributary of the River Rhine.

The Dutch Ministry of Infrastructure and Water Management provides 24/7 continuous monitoring of the water quality of the rivers Rhine and Meuse on two monitoring pontoons, using an Early Warning System (EWS). These monitoring stations are strategically located at the Dutch borders where the River Rhine and Meuse enter The Netherlands: Lobith (NL) /Bimmen (D) for the Rhine, and Eijsden (NL) for the Meuse. Three drinking water companies, which abstract water from the Meuse, monitor the quality of the river water and treated water as well. These monitoring strategies combine biological and chemical techniques, including the use of flow cytometry (algae composition and activity), water flea *Daphnia magna* and mussel monitoring system (*Dreissena bugensis*) as a biological EWS. Chemical and physical parameters, as well as organic contaminants, are also measured using a range of techniques such as purge and trap gas chromatography coupled to mass spectrometry (P&T-GC-MS), solid-phase extraction coupled to GC-MS (SPE-GC-MS), high-performance liquid chromatography coupled to a diode array detector (HPLC-DAD). HPLC-DAD is particularly useful as a screening technique due to its robustness, affordability, and compatibility with other early warning systems. The combination of chemical screening techniques

and biological early warning systems facilitates the early detection of incidental contamination, triggering alarm systems and allowing for measures to be taken to protect the drinking water supply and the river's ecosystem. The online HPLC-DAD method provides screening data within a few hours after analysis, allowing for rapid sharing of information when needed, to the water suppliers downstream. After all, protection of drinking water supply is only successful if monitoring can be carried out real-time, and findings are reported rapidly and efficiently.

The HPLC-DAD method described in this manuscript originates from the System for the Automated Monitoring of Organic Pollutants in Surface water (SAMOS). This is a fully automated system with online SPE to introduce large sample volumes on a GC(-MS) or LC(-MS), for which also the configuration comprising a sample preparation unit (PRO-SPEKT precolumn exchange unit; PRO-grammable Online Solid-Phase E(K)straction Techniques; Spark Holland, Emmen, The Netherlands), an LC system and a DAD detector is described in literature.^{2,3} The system proved its suitability for detecting polar pesticides in various European rivers, and it was shown that at least 50–100 organic micropollutants can be determined at ca. 1 $\mu\text{g/L}$. Several studies have shown its robustness and practical usefulness for real-time monitoring of

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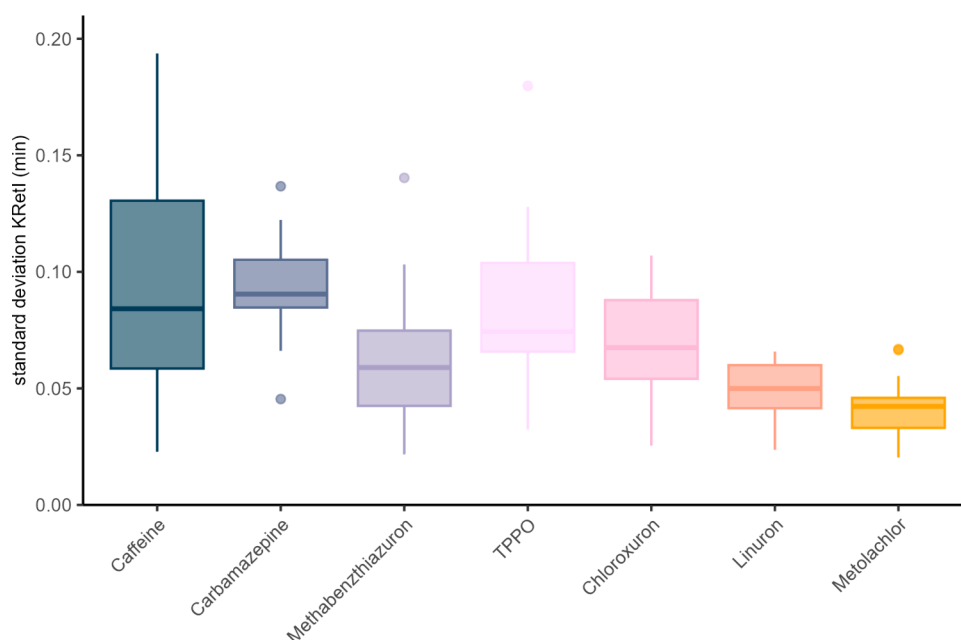


Figure 1. Standard deviation of the KRetI's (retention time index) by compound. The KRetI values of the standard compounds increase from left to right. The standard compounds are the compounds used in the interlaboratory study to compare the methods of the laboratories.

polar pesticides in river surface water.^{2–14} The method was implemented at the monitoring stations of Eijsden (Meuse River) and Lobith (Rhine River) by the former Dutch advisory body for Rijkswaterstaat in The Netherlands, the RIZA (Institute for Inland Water Management and Wastewater Treatment), in collaboration with the VU University of Amsterdam. Since 1999, this method has been further developed and harmonized together with drinking water laboratories. To enable the comparison and exchange of results, a normalized UV/vis spectrum library was created.¹⁵ Together with a simple linear retention index based on the Kováts index,¹⁶ this has led to a harmonized procedure used by all participating laboratories. This facilitated the resolution of several incidents impacting the drinking water supply. The standardized HPLC-DAD setup has been effectively used as a robust and cost-effective early warning system. An open-source R-Shiny app “HPLC-UV2R” has been developed to further optimize the exchange of libraries, which allows for the storage and sharing of normalized UV/vis spectra. This app is freely available through https://github.com/KWR-Water/HPLC-UV2R_public under a CC-BY-SA-4.0 license.

METHOD HARMONIZATION

In general, harmonizing may require a strict protocol on sample preparation, column type, mobile phase composition, column temperature, and exact gradient.

In this method, two internal standards are used to calculate retention time indices. To ensure interlaboratory comparability, we applied a protocol specifying the column type, mobile phase composition, and gradient conditions. Harmonization of these parameters is essential for aligning chromatographic data within the retention time window defined by the internal standards. For extrapolation beyond this window, strict adherence to the protocol is critical to maintain accuracy and reproducibility. Within the defined window, however, limited flexibility can be tolerated without compromising comparability. Acetonitrile is used as an organic solvent which

has a higher elution strength and lower UV-cutoff than for example methanol.^{17,18} The low UV cutoff is crucial to maintain low baseline noise in the lower wavelength part of the spectrum. Additionally, formic acid as a proton donor is added to be able to transfer/hyphen the method easily to mass spectrometry. For harmonization purposes, a set of main method parameters was agreed upon. The basic principle consisted of an online SPE followed by a reversed-phase separation with a linear gradient consisting of water and acetonitrile, both with formic acid (0.05% (v/v)) added as a modifier. Separation is achieved on a C18 reversed-phase column (C18, 250 mm × 4.6 mm i.d.) with a particle size (5 μm) to accommodate the large sample loading. A diode array detector operating at 1 nm step size between 200 and minimal 300 nm is used. The sample volume is not restricted, but in general participants use between 20 and 100 mL. The samples are filtered, formic acid is added (0.05% (v/v)) and internal standards (fenuron, chloroxuron, and neburon) are added at a final concentration of 1 μg/L. A preconcentration column (20 mm × 4.6 mm (i.d.)) packed with SPE sorbent (OASIS HLB or an equivalent thereof) is installed instead of the common sample loop in the HPLC system. The SPE column was loaded with the sample at a flow of 1.5–2.0 mL/min. After loading of the sample, the SPE column is eluted in a backward direction toward the analytical column protected by the guard column, which is an essential piece for the online SPE setup. The column temperature is maintained at 20 °C. The gradient must be linear until a 100% organic phase has passed. The total analysis time is long (87 min including the online SPE isolation of 20 mL sample) compared to today's standards. However, for EWS purposes, this is not an obstacle.

In addition to the standard detector built-in wavelength accuracy check, the wavelength accuracy of the detectors is also verified by a direct infusion of an erbium(III) perchlorate UV Wavelength Accuracy solution (Waters Milford, United States) and measuring the absorbance peak at 255.10 nm. Any observed deviations are used to correct the UV/vis spectra from this detector by adding or subtracting the difference

between the measured and reference wavelengths. In this way, the spectra are standardized across detectors and aligned with the spectral database. Another reason for performing the erbium test is that it is an external reference solution. By measuring erbium absorption bands across the UV–vis range, one can directly compare the wavelength accuracy of different detectors against the common standard. This enables the detection and correction of system-to-system differences, thereby establishing a common calibration basis for harmonization across instruments.

As part of the harmonization, a retention time index was developed as well. This KWR retention time index, called “KRetI” (eq 1), involves two internal standards: fenuron and neburon.¹⁵

$$\text{KRetI} = Rt_y = Rt_{F_n} + \frac{(Rt_{N_b} - Rt_{F_n})}{(Rt'_{N_b} - Rt'_{F_n})}(Rt_x - Rt'_{F_n}) \quad (1)$$

with Rt_y being the corrected retention time of compound A, Rt_x being the measured retention time of compound A, and Rt_{F_n} and Rt_{N_b} being the confirmed retention times of the internal standards fenuron and neburon, respectively. Rt'_{F_n} and Rt'_{N_b} are the measured retention times of these internal standards. The implementation of the KRetI allows the comparison of data between different laboratories, as the same compounds will have similar KRetI's regardless of the laboratory. This is especially crucial for the identification of unknown compounds.

The method is regularly tested by means of an interlaboratory study. Seven compounds (caffeine, carbamazepine, methabenzthiazuron, triphenylphosphine oxide (TPPO), chloroxuron, linuron, and metolachlor) are used to determine the comparability of the KRetIs. Supporting Information Figure S1 shows the standard deviations of these compounds determined during the yearly ring survey since 2010. The results indicate that the method is well-harmonized and comparable. Moreover, there is a linear relationship between the KRetIs and the standard deviation of the KRetIs (Figure S2). The slope of linear regression is significantly different from zero ($p < 0.05$, tested with a one-sample test of a major axis slope). As shown in Figure 1, the larger the KRetI, the smaller the standard deviation. Consequently, the highest mean standard deviations of the KRetIs are observed for the more polar compounds that elute first. This effect primarily arises from the way the KRetI is calculated. Fenuron elutes at approximately 18 min, whereas neburon elutes between 40 and 43 min. Because linear extrapolation is applied, greater extrapolation (corresponding to earlier elution in the chromatogram) results in increased deviation. A possible solution for this could be the employment of an additional reference standard at the beginning of the chromatogram. A suitable “natural marker” that is almost always detected in surface water, such as caffeine, could potentially be used for this evaluation. However, in practice, incorporating an additional selected and “added” KRetI compound would make the approach more robust and reliable.

■ WHY SHOULD HPLC-UV DAD NOT BE UNDERRATED?

The online-SPE-HPLC-DAD platform has proven its value regarding the early warning, monitoring, and screening of organic micropollutants in surface waters over the years. The power lies in its ability to provide real-time monitoring data,

since timely detection is crucial for protecting public health. Rapid notification of the authorities in case of detected concentrations of toxic compounds exceeding established signaling and alarm thresholds is imperative for risk mitigation associated with the abstraction of contaminated water. Currently, novel analytical techniques like nontarget screening using high-resolution mass spectrometry are of high interest for environmental monitoring purposes. One could argue that it would be more efficient to implement techniques such as LC-HRMS directly at monitoring stations, but these are much less robust, more costly, and require a much higher level of expertise from the operating staff and specific site requirements. In contrast, the site requirements for an HPLC-DAD configuration are less strict, and the system is proven to be robust under variable conditions, it is relatively simple to operate, and data processing is less complex. Data interpretation is less complex, and processing time of HPLC-DAD data is much shorter compared to HRMS. All in all, currently, HPLC-DAD is in addition to other more elaborate techniques a powerful and very suitable analytical technique for early warning and surface water monitoring on-site. A few examples of the vital role of HPLC-DAD for water quality monitoring in The Netherlands, are given below.

Managing Potential Risks: Terbutylazine, 2023. On March 6, 2023, the monitoring station in Eijsden issued an alarm notification concerning the presence of the herbicide terbutylazine in the Meuse, detected by the SPE-HPLC-DAD early warning system. The spectral and KRetI information on terbutylazine was available in the shared UV/vis-database, allowing for rapid identity using the HPLC-UV2R tool. The compound was quantified at 1.5 $\mu\text{g}/\text{L}$, by means of an external reference calibration standard. As terbutylazine is mainly used as herbicide, it is expected to be emitted during/after its use in agriculture. However, the detected concentration suggested an amount of pollution unlikely to be caused by agricultural use, but rather by an incidental large spill. Authorities were informed, and three Dutch drinking water companies paused the abstraction of water from the Meuse, or switched to extraction points in adjoining rivers, thereby effectively managing the potential risks for drinking water quality.

Initiating Legal Action: Prosulfocarb, 2019. On October 28, 2019, the monitoring station in Eijsden issued an alarm concerning an unknown compound. The compound was detected by means of the SPE-HPLC-DAD system with an estimated concentration of ca. 4 $\mu\text{g}/\text{L}$, based on the relative response to chloroxuron. A match was found with an unknown compound in the library that was previously detected in 2017. Two days later, another participating laboratory was able to identify the compound as prosulfocarb, by means of UPLC-HRMS. On November third, prosulfocarb was detected at an estimated concentration of 20 $\mu\text{g}/\text{L}$ at Eijsden and on November fourth, detected at 12 $\mu\text{g}/\text{L}$ near Roosteren. These values exceed the drinking water safety levels by more than 2 orders of magnitude. Accordingly, three drinking water companies extracting water from the river Meuse stopped their water intake. The extreme concentrations ruled out a ‘normal’ spill or diffuse emission source. Therefore, a collaboration was established between Rijkswaterstaat, the different drinking water companies, the Association of river water works – section Meuse (RIWA-Meuse), agricultural companies, and the Public Service of Wallonia (PSW; Belgium), in order to find the source of the spill. However, these efforts were not successful.¹⁹ The following months, prosulfocarb was not

detected above quantification limits, until August 2021 when Rijkswaterstaat detected concentrations $>0.5 \mu\text{g/L}$ in Eijsden. Consequently, additional sampling was carried out in the Meuse in Wallonia and these samples were measured for prosulfocarb by means of LC-HRMS. These analyses revealed also the presence of the fungicide propamocarb. This time, due to the collaboration between Rijkswaterstaat and PSW, the source of the contamination was determined to be a company in Wandre, Belgium, and legal action was initiated.

Joining Complementary Forces with HRMS: Pyrazole.

In 2015, three Dutch drinking water companies had to stop their intake from the river Meuse due to the presence of an unknown, relative polar compound at elevated concentrations ($33 \mu\text{g}$ internal standard equivalents/L). The first alarm came from a mussel monitor, followed by the HPLC-DAD, showing the occurrence of a highly UV-active compound. The water sample was dispatched and measured with the SPE-HPLC-DAD system hyphenated to an Orbitrap Fusion Tribrid (Thermo Fisher Scientific) with heated electrospray ionization (HESI). With this approach, the KRetI was used to mine the full scan (MS1) data on the compound of interest. Unfortunately, by means of SPE-HPLC-DAD-HESI-Orbitrap setup the compound was not visible, and therefore the sample was reanalyzed with atmospheric pressure ionization. At the same KRetI value as the UV/vis signal, a clear signal was detected in full scan mode with a protonated mass of m/z 69.04462. The empirical formula determined was undoubtedly $\text{C}_3\text{H}_4\text{N}_2$. A ChemSpider search revealed 21 possibilities, but based on the high polarity and structural properties, only two compounds remained as suspects. The identity of pyrazole (a byproduct of acrylonitrile production) was confirmed by means of a reference standard. Quantification led to detected concentrations of $90\text{--}100 \mu\text{g/L}$. The emission source could be identified: the compound was emitted by a plant on a nearby industrial site and came into the tributary via a malfunctioning industrial wastewater treatment plant. Concentrations did not lower sufficiently, and legal action was initiated.

MDMA. On a yearly basis, production locations for synthetic drugs are encountered in The Netherlands. Typically, this concerns the production of MDMA, amphetamine, and/or methamphetamine. Thirty production locations were encountered in 2011 and in 2023 this figure has risen to 151.^{20,21} The chemical waste from the production is a mixture of solvents, acids and bases contaminated with (pre)precursors, intermediate products, byproducts and end products.²² The waste is generally discarded in closed containers but in some cases also directly in sewer or surface water. The end products are controlled compounds and indicators for the fly tipping of drug waste in a waterbody. To buy, store and analyze these compounds a special license and compulsory rigorous administration is needed. However, the advantage of a common database is that a licensed laboratory can acquire the UV/vis spectra and share them through the database with other laboratories. This means, that it is not necessary for each laboratory to purchase these restricted reference compounds. On the sixth of June 2012, P&T-GC-MS revealed high levels of acetone at the monitoring station in Lobith (river Rhine). Back calculation based on river flow and measured concentration estimated the amount of acetone to be between 500 and 1000 L. In a biomonitoring cage with larvae, these larvae were showing abnormal behavior as a result of the high concentrations. The concentration of MDMA was quantified at $1.8 \mu\text{g/L}$ by means of off-line SPE LC-MS,²³ while a normal

concentration for the river Rhine is $<5 \text{ ng/L}$. By measuring more time proportional samples upstream, the location of the discharge could be located. Retrospective analysis of the HPLC-UV data showed that the presence of MDMA could be confirmed based on the KRetI value and the UV/vis spectrum.

HPLC-UV2R Database tool. Initially the shared library was created as a pseudo mass spectral database using NISTMS Search 2.0 software as a tool to compare and search unknown spectra. To facilitate this, an in-house tool to convert UV/vis text-based files to a normalized NIST format²⁴ was developed. With this tool, wavelength correction and a rough normalization were applied and metadata was added (e.g., CAS number, KRetI and origin). By using the “Reversed Search” within NIST, a newly imported spectrum could be searched within this NISTMS pseudo UV/vis database. Recently, a new tool has been developed to incorporate the normalization, conversion and database search. The basic text file format guidelines of the NIST format were kept. The new UV/vis library was developed based on a simple R Shiny application (CC-BY-SA-4.0 license) from Dr. Witting.²⁵ The result was an open-source R-script that runs a Shiny application; an interactive GUI where the user can search and upload UV/vis spectra, accompanied by relevant metadata. The script is compatible with UV/vis spectra from Empower (Waters software, v2.1–3.0) and OpenLab ChemStation (Agilent software), as well as various different file formats (.dx, .pda, .dif, or.msp). Spectra can be uploaded, they will be normalized automatically and a retention time index is calculated based on the user-specified retention times of neburon and fenuron. The spectra can be screened against databases and stored in user libraries. Database searches are performed based on retention index matches and/or overlapping λ_{max} values. Depending on the research question, the appropriate search mode can be selected. The added value of a common and shared library which can be shared between laboratories goes beyond comparing unknowns. UV/vis spectra of licensed or restricted compounds can easily be shared, without the need for every laboratory to apply for such a (costly) license. Examples of these compounds are opioids or precursors for several kinds of drugs of abuse and other chemical compounds with restricted use.

CONCLUSIONS

In The Netherlands a harmonized HPLC-DAD screening method with a shared spectral database is applied successfully. This method provides a robust early warning system for surface water quality. The robust and low-cost technique is able to raise an alarm when elevated concentrations of (un)known contaminations are detected. It thereby proves its suitability for early warning and its ability to provide valuable information for further research. In contrast to more advanced techniques such as LC-HRMS, the site requirements for an HPLC-DAD configuration are less strict, the configuration is more robust and easier to operate, and the data are easier to interpret. The presented open source HPLC-UV2R database tool (CC-BY-SA-4.0 license, https://github.com/KWR-Water/HPLC-UV2R_public) in combination with the harmonized method and KRetI retention time index allows for rapid comparison between data of different laboratories, and identification of compounds, thereby proving its value as an early warning system. The terbuthylazine, prosulfocarb, pyrazole and MDMA cases are examples which show the importance and added value of the harmonized SPE-HPLC-

DAD platform and the associated joint network of laboratories. The harmonized method and the database tool facilitated the collaboration between the different parties. Other laboratories adhering to the harmonized method could become part of this network.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsestwater.5c01116>.

Additional figures on KRetI values (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Patrick S. Bäuerlein – KWR Water Research Institute, 3430 BB Nieuwegein, The Netherlands; orcid.org/0000-0002-1110-5997; Email: Patrick.Baerlein@kwrwater.nl

Authors

Nienke Meekel – KWR Water Research Institute, 3430 BB Nieuwegein, The Netherlands; Analytical Chemistry for Environment and Health, Amsterdam Institute for Life and Environment (A-LIFE), Vrije Universiteit Amsterdam, 1081 HV Amsterdam, The Netherlands; orcid.org/0000-0002-8766-455X

Marijke W. de Bar – Rijkswaterstaat, Ministry of Infrastructure and Water Management, 8224 AD Lelystad, The Netherlands

Erik Emke – KWR Water Research Institute, 3430 BB Nieuwegein, The Netherlands; orcid.org/0000-0002-8441-1709

Martijn M. Pijnappels – Rijkswaterstaat, Ministry of Infrastructure and Water Management, 8224 AD Lelystad, The Netherlands; orcid.org/0009-0000-8081-2356

Runa Kooper-Mookerji – Aqualab Zuid, 4250 DC Werkendam, The Netherlands

Peter van Diepenbeek – Waterleiding Maatschappij Limburg, 6201 BB Maastricht, The Netherlands

Astrid Fischer – Department of Technology & Sources, Evides Water company, 3063 NH Rotterdam, The Netherlands; Faculty of Civil Engineering and Geosciences, TU Delft, 2600 GA Delft, The Netherlands

René van Doorn – KWR Water Research Institute, 3430 BB Nieuwegein, The Netherlands

Asmail Asgadaouan – KWR Water Research Institute, 3430 BB Nieuwegein, The Netherlands

Complete contact information is available at:

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Author Contributions

◆ M.W.d.B. and E.E. contributed equally to this work. CRediT: Nienke Meekel data curation, formal analysis, software, visualization, writing - original draft; Marijke de Bar investigation, methodology, writing - original draft, writing - review & editing; Erik Emke conceptualization, data curation, methodology, software, validation; Martijn Pijnappels conceptualization, investigation, methodology, writing - original draft; Runa Kooper-Mookerji investigation, methodology, writing - original draft; Peter van Diepenbeek conceptualization, methodology; Astrid Fischer methodology, writing - original draft; René van Doorn investigation, methodology, validation; Asmail Asgadaouan methodology, validation;

Patrick Steven Bäuerlein methodology, project administration, supervision, validation, writing - original draft, writing - review & editing.

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Notes

The authors declare no competing financial interest.

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