**Abstract:**

Background: Intravenous fluid warming devices with surface heating systems transfer heat using aluminum blocks, which if uncoated elutes toxic levels of aluminum into the infusate. This study examined extractable aluminum detected from long-term use of the enFlow® 202 device, which uses a parylene coating over its aluminum heating block. Methods: Bench testing involved 16 clinically relevant challenge fluids warmed at 40°C via continuous flow (0.2 and 5.5 ml.min⁻¹) for 5 hours or in a closed system that was gently rocked for 72 hours. Aluminum concentrations were measured using standard analytical chemistry techniques. Measured aluminum concentrations were compared to Tolerable Exposure limits to calculate Margins of Safety. A parallel in vivo animal study was performed using mice injected with fluids warmed by the enFlow 202.

Results: The enFlow 202 demonstrated low toxicological risks in all tests. Dynamic tests at two different flow rates with three challenge solutions resulted in concentrations less than the reporting limits (50 or 100 μg.l⁻¹) of the analysis method. The animals in the in vivo study showed no evidence of toxicity.

Conclusions: Observed toxicological risk levels associated with the enFlow 202 intravenous fluid warmer were below those set by the FDA and other regulatory bodies and suggest that the use of enFlow 202 is safe with a variety of IV solution types and in different therapeutic scenarios.
TYPE OF ARTICLE: Original Article

Fluid Warming with enFlow 202: Evaluation of Aluminum Extraction After Long-term Use

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SHORT TITLE:
enFlow 202 Fluid Warming and Extractable Aluminum
ABSTRACT

Background: Intravenous fluid warming devices with surface heating systems transfer heat using aluminum blocks, which if uncoated elutes toxic levels of aluminum into the infusate. This study examined extractable aluminum detected from long-term use of the enFlow® 202 device, which uses a parylene coating over its aluminum heating block.

Methods: Bench testing involved 16 clinically relevant challenge fluids warmed at 40°C via continuous flow (0.2 and 5.5 ml.min⁻¹) for 5 hours or in a closed system that was gently rocked for 72 hours. Aluminum concentrations were measured using standard analytical chemistry techniques. Measured aluminum concentrations were compared to Tolerable Exposure limits to calculate Margins of Safety. A parallel in vivo animal study was performed using mice injected with fluids warmed by the enFlow 202.

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Conclusions: Observed toxicological risk levels associated with the enFlow 202 intravenous fluid warmer were below those set by the FDA and other regulatory bodies and suggest that the use of enFlow 202 is safe with a variety of IV solution types and in different therapeutic scenarios.

KEYWORDS: Hypothermia: prevention; Anesthesia; Aluminum toxicity; Fluid warming; enFlow
Introduction

Maintaining a constant body temperature during anesthesia prevents major complications and prolonged hospitalisation (Kurz et al., 1996, Rajagopalan et al., 2008). Therefore, patient-specific temperature management is a major imperative during operative procedures. A drop of body core temperature below 36°C meets the criterion of hypothermia (Sessler, 1997). To help prevent such a decline in core temperature, several intravenous fluid warmers are used in the operating room to warm intravenous fluids. Most warming systems use a disposable cartridge containing a heating block to warm the fluid up to 40°C (O’Neill et al., 2001, Shao et al., 2012).

Some brands of intravenous fluid warmers using aluminum heating blocks have been shown to leach potentially significant amounts of aluminum into the infusate. One group (Perl et al., 2019) studied a fluid warming device with a coated aluminum heating block (Fluido® Compact, The 37°Company, Amersfoort, the Netherlands) and an uncoated device (enFlow®, Vyaire Medical Inc, Mettawa, IL, USA). The researchers pumped two different infusion solutions (saline and a balanced electrolyte solution) through the two systems for 60 minutes and evaluated the leached aluminum. They found an increased and potentially unacceptably high level of leached aluminum when using the uncoated system. A second study examined the uncoated enFlow but with blood products as well as an electrolyte product for 60 minutes (Taylor et al., 2019). This study confirmed that the enFlow warmer also leached potentially dangerous levels of aluminum into the warmed IV fluids. Cabrera et al. recently evaluated the aluminum leaching from the Level 1® H-1025 Fast Flow Fluid Warmer (Smiths Medical, Minneapolis, MN, USA) (Cabrera et al., 2020). The authors evaluated three perfusion solutions: saline; Ringer’s lactate; and heparinised whole blood, at a constant flow rate of 30 ml.min⁻¹ over 60 minutes. They found that the amount of aluminum leached from the system did not reach clinically significant levels, although their findings were subject to debate (Cabrera and Borton, 2020, Exley, 2020, Perl et al., 2020).
The original enFlow fluid warmer was recently redesigned with a parylene coating to the fluid-contacting portion of the aluminum heating block. This redesigned device, known as the enFlow 202 (Figure 1), is identical to the original uncoated enFlow except for the parylene coating applied to the aluminum heating blocks.

Previous studies evaluated fluid warming devices only for a relatively short time (60 minutes) using only a few intravenous fluids (Cabrera et al., 2020, Perl et al., 2019, Taylor et al., 2019). This study evaluates potential aluminum leaching and its toxicity after a prolonged (72 hours) exposure and for 16 different clinically relevant fluids to simulate a worse-case scenario of a patient having multiple surgeries and with various solutions. We evaluated both lipophilic and hydrophilic fluids with chronic exposures that exceed manufacturers’ recommendations. Additionally, available literature does not address in vivo correlates of toxicity or biological effects that may arise related to the fluid warmer, so we also performed an in vivo preclinical study in mice using both hydrophilic and lipophilic heated fluids from the enFlow 202. We hypothesised that the coated enFlow 202 system does not result in a significant leaching of aluminum into heated fluids as measured by toxicity assessment.

**Methods**

We performed three different experiments for this study: dynamic flow fluid analysis; long-term quasi-static fluid analysis; and in vivo animal testing in mice.

**Bench Testing (dynamic and quasi-static testing)**

Two different bench setups and durations were tested: “dynamic” and “quasi-static” (Figure 2). During dynamic testing, challenge fluids were flowed through the enFlow 202 cartridge at a fixed flow rate for 5 hours and the outputted fluids were collected and tested for aluminum concentration. Device warming was activated for the duration of the testing at the fixed temperature of 40°C. For quasi-static testing, methods based on the principles described in ISO 10993-18:2005 were followed (Food and Drug
Administration, 2017, International Organization for Standards, 2005). Specifically, an enFlow 202 cartridge was filled with one of the challenge solutions and capped closed. The cartridges were then placed inside a temperature chamber at 40 °C and gently rocked continuously for 72 hours.

Challenge Solutions

For dynamic testing, three challenge solutions were examined: Sterofundin ISO, Plasma-Lyte 148, and whole blood. Each solution was tested at two different flow rates: 0.2 ml.min⁻¹ for neonates and 5.5 ml.min⁻¹ for adults. For quasi-static testing, 16 frequently used IV solutions were tested: single donor human whole blood; human buffy coat; human packed cells; human plasma diabetic type 2; human platelet lysate; 5% dextrose solution; 3% sodium chloride injection; Plasma-Lyte 148; Ringer’s lactate in 5% dextrose; Sterofundin ISO; human serum albumin 25%; normal human serum off-the-clot charcoal-dextran 1; human cord blood; leukocytes; potassium chloride in 5% dextrose and 0.9% sodium chloride; and 10% dextrose and 0.45% sodium chloride. For the first ten challenge solutions listed above, quasi-static testing was also conducted on the uncoated enFlow device for direct comparison with the enFlow 202 results.

Analytical Chemistry

Post-warming, the aluminum concentration within challenge fluids was determined using inductively coupled mass spectroscopy (ICP/MS). The aluminum preparation and analyses for each sample of challenge fluids used matrix spikes, matrix spike duplicates, and matrix blanks in addition to the typical analytical laboratory quality control samples. Since the matrices used may have had inherent aluminum, all results were matrix blank corrected to determine device-related extractable aluminum amounts.

Establishing acceptance criteria for dynamic and static testing

TOLERABLE INTAKE AND TOLERABLE EXPOSURE
To determine the toxicological hazard of the enFlow 202, we compared the measured aluminum concentrations to the Tolerable Exposure (TE) levels for aluminum estimated based on guidelines described in ISO 10993-17:2012 (International Organization for Standards, 2009). TE levels represent the maximum dose at which exposure to the substance does not produce adverse events or pose an unacceptable risk to human health (International Organization for Standards, 2012). In this study, we estimated TEs for acute and chronic exposure for four patient subgroups: adult males, adult females, paediatrics, and neonates.

TE is derived based on the Tolerable Intake (TI) level for the particular exposure duration and patient subgroup. TIs are estimated from experimental values shown to be without adverse effects, known as the No Observed Adverse Effect Level (NOAEL), and Uncertainty Factors (UFs), which are safety factors that account for pharmacokinetic, toxicokinetic, and metabolic differences among exposed people.

Specifically, TI is quantified as:

\[ TI = \frac{NOAEL}{UF_1 \times UF_2 \times UF_3}. \]

The UFs include modifications for inter-individual variation among people (UF1), extrapolation of effects between animals and people (UF2), and the quality and relevance of the experimental data (UF3).

In addition to these UFs within the TI estimation, the TE calculation includes another correction factor known as the Utilization Factor (UTF). UTF is the product of two exposure factors: Concomitant Exposure Factor (CEF) which accounts for device use frequency, and Proportional Exposure Factor (PEF) which accounts for potential exposure to leachables from other sources. TE was calculated as the product of TI, patient body mass (mB, in kg), and UTF:

\[ TE = TI \times mB \times UTF. \]
The default values of CEF (0.2) and PEF (1.0) specified in ISO 10993-17:2012 were used (International Organization for Standards, 2012). According to that standard, the default body weight for adult male, adult female, paediatrics, and neonates are specified as 70 kg, 58 kg, 10 kg and 3.5 kg, respectively.

For the acute exposure case, the study adopted 850 μg.dose\(^{-1}\), the FDA acceptable parenteral limit for biological products, and adjusted by body weight to yield a worst-case acute exposure TI (European Food Safety Authority World Health Organization, 2016). Using these limits, the calculation for the acute contact duration in adult males was:

\[
TI = 850 \mu g \times 70 \text{ kg}^{-1} = 12.1 \mu g.\text{kg}^{-1},
\]

\[
TE = 12.1 \mu g.\text{kg}^{-1}.\text{day}^{-1} \times 70 \text{ kg} \times 0.2 = 170 \mu g.\text{day}^{-1}.
\]

For chronic contact exposures beyond 24 hours in paediatrics and adults, the study used the most conservative chronic oral tolerable daily intake (TDI) from the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) of 0.3 mg.kg\(^{-1}\).day\(^{-1}\) as the NOAEL to calculate TI (Scientific Committee on Health Environmental and Emerging Risks (SCHEER EU), 2017). The SCHEER TDI already accounts for inter-individual variation among people (UF1) and the extrapolation of effects between animals and people (UF2) and therefore we assigned each a value of 1. A value of 100 was assigned to UF3 based on FDA guidance to account for the difference between chronic oral and IV exposure (Food and Drug Administration, 2015):

\[
TI = \frac{0.3 \text{ mg.kg}^{-1}.\text{day}^{-1}}{1 \times 1 \times 100} = 3.0 \mu g.\text{kg}^{-1}.\text{day}^{-1}
\]

\[
TE = 3.0 \mu g.\text{kg}^{-1}.\text{day}^{-1} \times 70 \text{ kg} \times 0.2 = 42 \mu g.\text{day}^{-1}
\]
For chronic contact exposures beyond 24 hours in neonatal populations, the limit was derived from the 25 μg.l⁻¹ limit acceptable to the FDA and the lowest daily total parenteral nutrition volume (0.060 l.kg⁻¹.day⁻¹) (Food and Drug Administration):

\[ TE = 25\mu g.l^{-1} \times 0.061 \text{l.kg}^{-1}.\text{day}^{-1} \times 3.5 \text{kg} = 5.25 \mu g.\text{day}^{-1}. \]

MARGIN OF SAFETY

To characterise the hazard associated with each substance, Margin of Safety was quantified as the ratio of TE to the measured aluminum concentration:

\[ \text{Margin of Safety} = \frac{TE}{\text{Measured Aluminum Concentration}} \]

Margin of Safety is unit-less index which indicates a fold-level difference between the threshold and measured exposure level. A Margin of Safety greater than 1.0 indicates low toxicological (International Organization for Standards, 2002). The worst-case Margin of Safety was calculated as the ratio between the TE and the challenge solution with the highest concentration of aluminum leached from the enFlow 202 device.

For the challenge solutions which were tested with both the uncoated enFlow and coated enFlow 202 device, the percent decrease in the measured aluminum concentration when using the enFlow to the enFlow 202 was quantified for each solution:

\[ \text{Percent Decrease} = \left( \frac{\text{Concentration}_{\text{enFlow}} - \text{Concentration}_{\text{enFlow 202}}}{\text{Concentration}_{\text{enFlow}}} \right) \times 100\% \]
In vivo animal testing in mice

In addition to the dynamic and quasi-static bench testing, preclinical acute systemic toxicity testing was conducted on mice using the enFlow 202 device to assess the potential health hazards associated with acute exposure using the warmed fluids from the device. Testing was performed at Nelson Laboratories, LLC, (Salt Lake City, UT, USA) in compliance with ISO 10993-11:2017 (International Organization for Standards, 2017) and ISO 10993-12:2012 (International Organization for Standards, 2012). The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee of American Preclinical Services, LLC, Minneapolis MN. A total of 20 male albino outbred strain mice (ten test mice and ten negative control mice) were used in the study. In test mice, use of the enFlow 202 device was simulated by injecting the mice with a solution (saline or sesame seed oil) that was previously heated and agitated inside an enFlow 202 cartridge. Preparation of control extracts was identical to test extracts but without the enFlow 202 cartridge. Test mice received a single 50 ml.kg\(^{-1}\) injection of the test extract and control mice received a single 50 ml.kg\(^{-1}\) injection of control extract on Day 0. For each group, five mice received extracts using normal saline via IV injection and five received extracts using sesame seed oil via intraperitoneal injection. Animal bodyweight was measured immediately prior to the injection (Day 0) and then daily for the next three days. Overall animal health and signs of acute toxicity were monitored at 4 ± 0.25 hours, 24 ± 2 hours, 48 ± 2 hours, and 72 ± 2 hours post-injection by comprehensive clinical observations by trained personnel. Specifically, the following were monitored: changes in skin and fur; eyes and mucous membranes; respiratory, circulatory, autonomic, and central nervous systems; and somatomotor activity and behavior patterns.

Means and standard deviations of the animal weights for the control and test groups were quantified for each injection solution at each measurement time. Percent change in bodyweight from time 0 to 72 hours post-injection was calculated for each animal. Two success criteria were defined prior to the start of the preclinical study. The first success criterion was that no animals in each five-animal test group
showed greater biological reactivity during the three-day observation period. The second success
criterion was that all the following were met for each five-animal test group: less than two animals died;
less than two animals experienced convulsions or prostration; and final bodyweight changed by less
than 10% in less than three animals.

*Independent and Dependent Variables*

For the bench testing, the independent variables were protocol type (i.e., dynamic vs. quasi-static),
challenge solution, and flow rate. The dependent variable was measured aluminum concentration. To
understand the hazard associated with each substance and four patient populations, we calculated
Margins of Safety by comparing these measured aluminum concentrations to Tolerable Exposure limits.

For the in vivo testing, we compared the physiological responses of mice that received injections
simulating the use of the enFlow 202 device to control injections without the enFlow 202 device. We
tested both intravenous and intraperitoneal injections. The dependent variables were animal
bodyweight, overall animal health, and signs of acute toxicity at 4, 24, 48, and 72 hours post-injection.

All data analyses were performed using Matlab (MathWorks, Natick, MA, USA).

*Results*

The concentration of aluminum in the solutions following dynamic testing using the coated enFlow 202
device was less than 50 μg.l⁻¹ for Sterofundin and Plasma-Lyte 148 solutions and less than 100 μg.l⁻¹ for
whole blood for both flow rates.

For quasi-static testing of the enFlow 202, the derived Margin of Safety values for aluminum were above
a value of 1.0. Table 1 compares the amount of aluminum detected in the 16 challenge IV solutions
heated at 40°C (104°F) for 72 hours with the uncoated enFlow device and parylene-coated enFlow 202
device. For challenge solutions that were tested with both the uncoated enFlow and coated enFlow 202,
the aluminum concentration decreased by at least 98.9% for all solutions except for 3% sodium chloride Injection USP (36.4% decrease). The aluminum concentration for this solution corresponds to a Margin of Safety of 6.0 for the coated enFlow 202.

Sterofundin ISO showed the highest aluminum concentration (3.11 μg.device⁻¹) compared to all tested fluids. Therefore, this concentration was used for evaluation of Margin of Safety. Margins of Safety were quantified for both acute and chronic patient contact and all four target populations (Table 2). For acute patient contact, the TE was based on the parental limit established by the FDA of 850 μg.dose⁻¹ (Food and Drug Administration). For chronic contact, TE was based on the TDI established by SCHEER (0.3 mg.kg⁻¹.day⁻¹) for adults and paediatrics (Scientific Committee on Health Environmental and Emerging Risks (SCHEER EU), 2017) and 25 μg.l⁻¹ for neonates based on the FDA’s recommended maximum for IV nutrition (Food and Drug Administration). Margins of Safety for both exposure durations and all populations were above 1.0. For acute use in adult patients, the Margins of Safety are 45.3 and 54.7 for females and males, respectively. Using the most conservative limit in a chronic use neonatal patient, the Margin of Safety for aluminum exposure is 1.7.

All 20 animals survived the preclinical testing and were in overall good health over the course of the study. Test animals, which received injections simulating use of the enFlow 202 device, showed no greater reaction to the injection compared to the control animals. The animals weighed between 25.5 and 34.4 g at the start of the study and none developed weight loss greater than 10% over the course of the study (Table 3).

Discussion

This study found that the coated enFlow 202 device, when used in both acute and chronic exposures, resulted in minimal aluminum elution and favorable derived Margin of Safety above values of 1.0, correlating with safe patient exposure levels that are below those set by the FDA and SHEER guidelines.
(Food and Drug Administration, Food and Drug Administration, Scientific Committee on Health Environmental and Emerging Risks (SCHEER EU), 2017). Dynamic tests at two different flow rates with three challenge solutions resulted in concentrations less than the reporting limits (50 or 100 μg.l\(^{-1}\)) of the analysis method, levels comparable with other marketed warming devices. This result is consistent with the finding from a previous study conducted on a different coated IV fluid warmer (Perl et al., 2019). In that study, the analysis method had a slightly less sensitive reporting limit of 128 μg.l\(^{-1}\) and the exposure was limited to 1 hour compared to 5 hours in this study.

In clinical use, IV fluid and blood warmers are used with a wide range of solutions such as saline and electrolyte solutions as well as blood and blood products. Each solution has unique thermochemical properties and interaction with the warmer’s cartridge and may therefore result in different amounts of aluminum leaching into the solution. The previous studies mentioned above examined aluminum exposure when using IV fluid warmers with a small subset of potential solutions. Our study expanded on these studies and measured aluminum elution after prolonged exposure to 16 different clinically relevant challenge fluids when using the enFlow 202. For ten of these 16 these fluids, the aluminum exposure was also tested using the uncoated enFlow device and compared to the exposure when using the enFlow 202.

Recent bench testing from other laboratories revealed potentially unsafe levels of aluminum leaching into solutions from the uncoated enFlow device (Perl et al., 2019, Taylor et al., 2019). Specifically, Perl et al. found an aluminum concentration of approximately 6000 μg.l\(^{-1}\) when flowing Sterofundin through an uncoated enFlow device (Perl et al., 2019). Taylor et al. expanded upon this study, examining aluminum concentrations for a total of five solutions. They found levels of aluminum exposure in Plasma-Lyte 148 and compound sodium lactate solutions that were comparable to those found in Sterofundin in a previous study (Taylor et al., 2019). The results of the current study confirmed that the parylene coating
on the cartridge significantly reduced the amount of leaching of aluminum into a wide range of clinically
relevant challenge solutions (see Table 1).

There are three significant strengths of this research. First is that we tested the enFlow 202 for
prolonged exposure to fluids. In general, fluid warmers in an individual patient could potentially be
required for time intervals of 1-12 hours, depending on the extent of the surgery and resuscitative
efforts. Difficult individual cases may then require repeated surgeries with renewed need for fluid
warming. Because of this, we chose to study the effects of 72 hours of exposure to enFlow. Secondly,
most studies have only addressed a few representative fluids, limiting the generalizability of their
research. We sought to evaluate the safety of this device over a much broader spectrum of fluids that
might actually be used in direct patient care. We chose 16 frequently used IV solutions that were
clinically relevant in anesthesiology from simple (saline) to complex (whole blood) and found no
evidence of aluminum leaching into the fluid using enFlow 202. Finally, most published studies lack in
vivo assessments of aluminum levels resulting from fluid warmers. Therefore, we added the studies on
mice to evaluate the potential impact of aluminum toxicity resulting from the use of the enFlow 202.
The current study was specifically designed to address the major concerns of practicing clinicians.

A limitation of our study is that the aluminum concentration reporting limit of our analysis method was
50 μg.l⁻¹ for Sterofundin and Plasma-Lyte 148 and 100 μg.l⁻¹ for whole blood. Therefore, in the dynamic
testing, it was not possible to differentiate between the measured aluminum concentration and the
most stringent FDA standard of 25 μg.l⁻¹. Regardless, the results of quasi-static testing show aluminum
concentrations under this threshold for all challenge solutions. We did not compare enFlow 202 to
devices other than the original enFlow using the same experimental setup, so no assertions can be made
about comparisons between other brands of devices. As mentioned, our test methods, while standard,
were different from those previously used with other warming devices, making direct comparisons to
other studies impossible. The default values of exposures specified in ISO 10993-17:2012 are based on
default body weights for males, females, children, and infants, and the standard infant weight (3.5 kg) exceeds values typical of premature neonates (for example, 500 grams to 2.5 kg). Finally, we used banked blood specimens rather than samples from a volunteer donor or actual patients, and the samples were measured in vitro rather than in vivo.

In summary, the results of these experiments indicate that observed toxicological risk levels associated with the enFlow 202 intravenous fluid warmer were below those set by the FDA and other regulatory bodies and suggest that the use of enFlow 202 is safe with a variety of IV solution types and in different therapeutic scenarios. The enFlow 202 showed marked improvement in safety compared to its predecessor, the enFlow.

Acknowledgments

Acknowledgements: Vyaire Medical, the manufacturer of enFlow 202, supported this study. Marion E Glick and Edward A. Rose, M.D., M.S.A. assisted in the preparation of this manuscript, and their services were paid for by Vyaire Medical. Edward Rose was given express consent by the authors to submit this manuscript on their behalf for publication.

Declaration of Conflicting Interests

MP is the medical director of Vyaire Medical. Vyaire Medical, the manufacturer of this device, funded this research but had no role in study design, data acquisition, or analysis. AW is an employee of Vyaire Medical.
References

CABRERA, J. & BORTON, L. 2020. Quantification of safe aluminium levels released into infusion solutions by the Level 1 Fast Flow Fluid Warmer: a reply. Anaesthesia, 75, 1253-1254.
CABRERA, J., BORTON, L. & BARRETT, G. 2020. Quantified aluminium levels released into blood and fluids using the Level 1 Fast Flow Fluid Warmer. Anaesthesia, 75, 271-272.
EUROPEAN FOOD SAFETY AUTHORITY WORLD HEALTH ORGANIZATION 2016. Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree. EFSA Supporting Publications, 13, 1006E.
EXLEY, C. 2020. Aluminium-based fluid warmers are not proven to be safe. Anaesthesia, 75, 833-833.

FOOD AND DRUG ADMINISTRATION. General biological products standards. Constituent materials. 21 CFR 610.15.a. April 1, 2019. [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=610.15 [Accessed 09/02 2020].

FOOD AND DRUG ADMINISTRATION. Labelling aluminium in large and small volume parenterals used in total parenteral nutrition. 21 CFR 201.323.a. 1 April 2013 [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=201.323 [Accessed 09/02 2020].

FOOD AND DRUG ADMINISTRATION 2015. Q3D elemental impurities guidance for industry. US Department of Health and Human Services, 41.

FOOD AND DRUG ADMINISTRATION. 2017. Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing within a Risk Management Process. 2016 [Online]. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and [Accessed October 9 2020].

INTERNATIONAL ORGANIZATION FOR STANDARDS. 2002. Biological Evaluation of Medical Devices—Part 17: Establishment of Allowable Limits for Leachable Substances (ISO 10993-17) [Online]. International Organization for Standardization Geneva, Switzerland. Available: https://www.iso.org/standard/23955.html [Accessed October 9 2020].

INTERNATIONAL ORGANIZATION FOR STANDARDS. 2005. ISO 10993-18:2005 Biological evaluation of medical devices — Part 18: Chemical characterization of materials [Online]. Available: https://www.iso.org/standard/41106.html [Accessed October 9 2020].

INTERNATIONAL ORGANIZATION FOR STANDARDS. 2009. 10993-1: 2009 Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process [Online]. Available: https://www.iso.org/standard/44908.html [Accessed October 9 2020].

INTERNATIONAL ORGANIZATION FOR STANDARDS. 2012. ISO 10993-12:2012 Biological evaluation of medical devices — Part 12: Sample preparation and reference materials [Online]. Available: https://www.iso.org/standard/53468.html [Accessed October 8 2020].
INTERNATIONAL ORGANIZATION FOR STANDARDS. 2017. ISO 10993-11:2017 Biological evaluation of medical devices — Part 11: Tests for systemic toxicity [Online]. Available: https://www.iso.org/standard/68426.html [Accessed October 8 2020].

KURZ, A., SESSLER, D. I. & LENHARDT, R. 1996. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med, 334, 1209-15.

O’NEILL, K. A., BERNARDO, L. M., GARDNER, M. J., LUCKE, J. & FORD, H. 2001. The effects of core and peripheral warming methods on temperature and physiologic variables in injured children. Pediatric emergency care, 17, 138-142.

PERL, T., KUNZE-SZIKSZAY, N., BRAUER, A., QUINTEL, M., ROHRIG, A. L., KERPEN, K. & TELGHEDER, U. 2019. Aluminium release by coated and uncoated fluid-warming devices. Anaesthesia, 74, 708-713.

PERL, T., KUNZE-SZIKSZAY, N., BRÄUER, A. & ROY, T. 2020. Quantified aluminium levels released into blood and fluids using the Level 1 Fast Flow Fluid Warmer. Anaesthesia, 75, 834-834.

RAJAGOPALAN, S., MASCHA, E., NA, J. & SESSLER, D. I. 2008. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. Anesthesiology, 108, 71-7.

SCIENTIFIC COMMITTEE ON HEALTH ENVIRONMENTAL AND EMERGING RISKS (SCHEER EU). 2017. Final opinion on tolerable intake of aluminium with regards to adapting the migration limits for aluminium in toys [Online]. Available: https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_009.pdf [Accessed October 9 2020].

SESSLER, D. I. 1997. Mild perioperative hypothermia. N Engl J Med, 336, 1730-7.

SHAO, L., ZHENG, H., JIA, F. J., WANG, H. Q., LIU, L., SUN, Q., AN, M. Y., ZHANG, X. H. & WEN, H. 2012. Methods of patient warming during abdominal surgery. PLoS One, 7, e39622.

TAYLOR, M., CHOI, D., FITZPATRICK, S. & GUNN, K. 2019. Characterisation of aluminium release by the enFlow® fluid-warming system in crystalloids and blood products. Anaesthesia, 74, 1374-1380.
Tables and Figures

**Table 1.** Quantitatively measured aluminum from fluids heated at 40 °C (104 °F) for 72 hours with the enFlow and enFlow 202 devices. As the challenge fluids may have inherent aluminum, results were matrix blank corrected to determine device-related extractable aluminum amounts. Results are sorted from lowest to highest enFlow 202 aluminum concentration.

| Fluid                                      | enFlow Blank Corrected (μg.device⁻¹) | enFlow 202 Blank Corrected (μg.device⁻¹) | Percent Decrease vs. enFlow |
|--------------------------------------------|-------------------------------------|------------------------------------------|----------------------------|
| Human Serum Albumin 25%, 100 mL             | --                                  | < 0.500                                  | NA                         |
| Single Donor Human Whole Blood             | 392                                 | < 0.833                                   | > 99.8%                    |
| Normal Human Serum Off-the-Clot, Charcoal-Dextran 1 | --                                  | 0.0200                                   | NA                         |
| Human Buffy Coat                            | 158                                 | 0.0450                                    | 100.0%                     |
| Human Cord Blood                            | --                                  | 0.0800                                    | NA                         |
| Human Packed Cells                          | 113                                 | 0.0900                                    | 99.9%                      |
| Human Plasma, Diabetic Type 2              | 1,310                               | 0.125                                     | 100.0%                     |
| 5% Dextrose Solution                        | 12.1                                | 0.133                                     | 98.9%                      |
| Leukocyte                                   | --                                  | 0.381                                     | NA                         |
| Human Platelet Lysate                       | 1,290                               | 0.731                                     | 99.9%                      |
| 3% Sodium Chloride Injection USP            | 1.41                                | 0.897                                     | 36.4%                      |
| Potassium Cl in 5% Dextrose & 0.9% Sodium Chloride | --                                  | 1.10                                      | NA                         |
| 10% Dextrose & 0.45% Sodium Chloride       | --                                  | 1.11                                      | NA                         |
| PLASMA - LYTE 148                           | 4.860                               | 1.32                                      | 100.0%                     |
| Lactated Ringer's & 5% Dextrose             | 479                                 | 2.62                                      | 99.5%                      |
| Sterofundin                                 | 376                                 | 3.11                                      | 99.2%                      |
Table 2. Margin of Safety Summary for Aluminum in Sterofundin ISO for acute and chronic patient contact and for four patient populations. Margin of Safety is defined as the ratio of the Tolerable Exposure to the measured Extractable Amount. A Margin of Safety greater than a value of 1.0 is indicative of low toxicological hazard.

| Target Population    | Weight (kg) | Tolerable Exposure (μg.day\(^{-1}\)) | Extractable Amount (μg.device\(^{-1}\)) | Margin of Safety |
|----------------------|-------------|-------------------------------------|----------------------------------------|-----------------|
| **Acute Patient Contact** |             |                                     |                                        |                 |
| Adult Male           | 70          | 170.0*                              |                                        | 54.7            |
| Adult Female         | 58          | 140.9*                              |                                        | 45.3            |
| Paediatric           | 10          | 24.3*                               |                                        | 7.8             |
| Infant               | 3.5         | 8.5*                                |                                        | 2.7             |
| **Chronic Patient Contact** |         |                                     |                                        |                 |
| Adult Male           | 70          | 42.0†                               |                                        | 13.5            |
| Adult Female         | 58          | 34.8†                               |                                        | 11.2            |
| Paediatric           | 10          | 6.0†                                |                                        | 1.9             |
| Neonates             | 3.5         | 5.25‡                               |                                        | 1.7             |

*Based on the parental limit for biologics established by the FDA of 850 μg.dose\(^{-1}\)

†Based on the TDI for chronic exposure established by SCHEER of 0.3 mg.kg\(^{-1}\).day\(^{-1}\)

‡Based on the limit of 25 μg.l\(^{-1}\) set forth by the FDA for neonatal intravenous nutrition
Table 3. Bodyweight of control and test animals given normal saline and sesame seed oil injections.

Bodyweights measured immediately before injection (Day 0) and 72 hours later are listed. The percent change from Day 0 to 72 hours were well less than 10% for all animals. Data are listed as mean (standard deviation).

| Injection        | Group   | Day 0 (g) | 72 Hours (g) | Percent Change (%) |
|------------------|---------|-----------|--------------|--------------------|
| Normal Saline    | Control | 30.3 (1.5) | 30.4 (1.2)   | 0.5 (1.5)          |
|                  | Test    | 30.5 (1.1) | 30.3 (1.6)   | -0.6 (1.9)         |
| Sesame Seed Oil  | Control | 30.6 (1.7) | 30.4 (1.6)   | -0.5 (2.1)         |
|                  | Test    | 30.0 (3.4) | 30.0 (3.4)   | 0.0 (1.1)          |
**Figure Captions**

**Figure 1.** enFlow 202 Disposable IV/Blood Warmer with parylene-coated aluminum warming plate of the patient-contacting disposable cartridge. Photograph courtesy of Vyaire Medical Inc, Mettawa, IL, USA.

**Figure 2.** A: Quasi-static testing, the enFlow 202 cartridge was placed in a heated temperature chamber at 40°C and gently rocked for 72 hours, B: Dynamic testing at a fixed flow rate for 5 hours.
Figure 1. enFlow 202 Disposable IV/Blood Warmer with parylene-coated aluminium warming plate of the patient-contacting disposable cartridge. Photograph courtesy of Vyaire Medical Inc, Mettawa, IL, USA.

1828x1219mm (72 x 72 DPI)
Figure 2. A: Quasi-static testing, the enFlow 202 cartage was placed in a heated temperature chamber at 40°C and gently rocked for 72 hours, B: Dynamic testing at a fixed flow rate for 5 hours.
(1) **Ethics approval**

Not applicable.

(2) **Informed consent**

Not applicable.

(3) **Trial registration**

Not applicable.