National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Injection needles

Fact finding and risk assessment of excess adhesive

RIVM Letter report 2015-0094
D. de Kaste et al.

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Injection needles

Fact finding and risk assessment of excess adhesive

RIVM Letter report 2015-0094
D. de Kaste et al.

Colophon

Laboratory investigations:
Peter van Aalst
Frank Bakker
Hans Cremers
Arjan van Drongelen
Robert Geertsma
Roelina Hoving
Riny Janssen
Dries de Kaste
Peter Keizers
Walther Klerx
Ellen Lamme
Peter van Lierop
Jeroen Pennings
Paul Schwillens
Marieke Slotboom
Bastiaan Venhuis

Risk assessment:
Janine Ezendam
Robert Geertsma
Lya Hernàndez
Joke Herremans
Paul Janssen
Wim de Jong
Peter Jongen
Henk van Loveren
Andre Muller
Kim Notenboom
Agnes Oomen
Dick Sijm

Contact:
Dries de Kaste
Centre for Health Protection
dries.de.kaste@rivm.nl

This investigation has been performed by order and for the account of IGZ, within the framework of Ad hoc project V/080118/15/IN.

This is a publication of:
National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl

Publiekssamenvatting

Injectienaalden

Feitenonderzoek en risicobeoordeling overtollige lijm

In opdracht van de Inspectie voor de Gezondheidszorg (IGZ) heeft het RIVM onderzocht of er overtollige lijm zit in twee typen injectienaalden van de firma Terumo (K-Pack II en Neolus). Het onderzoek toont aan dat in minder dan 1 procent van de Terumo naalden zichtbaar overtollige lijm is aangetroffen (epoxyhars). Dit percentage is veel lager dan het percentage van 20 procent dat in het actualiteitenprogramma EenVandaag[1] is genoemd. Het RIVM heeft voor dit onderzoek ruim 7000 naalden onderzocht.

Het RIVM heeft ook naalden van andere fabrikanten onderzocht. Daarin is eveneens overtollige, uitgeharde lijm aangetroffen, in een vergelijkbaar klein percentage als bij de Terumo-naalden. Er zijn geen volledig geblokkeerde naalden aangetroffen. Ook is in de onderzochte naalden geen vloeibare lijm waargenomen.

Vervolgens heeft het RIVM beoordeeld in hoeverre de overtollige lijm een risico vormt voor de gezondheid van de patiënt. Dit is gedaan op basis van een worst case scenario, waarbij er onder andere van uit is gegaan dat er niet-uitgeharde lijm wordt geïnjecteerd. Van de geëvalueerde stoffen die in de lijm zijn verwerkt, worden geen gezondheidseffecten verwacht. Alleen van titaandioxide (witte kleurstof) is dat niet met zekerheid vast te stellen, maar de kans op negatieve effecten wordt op basis van de testresultaten van de naalden die zijn onderzocht, als heel klein beschouwd. De kans op negatieve effecten van deeltjes uitgeharde lijm wordt eveneens als heel klein beschouwd.

Tijdens het onderzoek zijn in de naalden van verschillende fabrikanten ook plastic deeltjes aangetroffen, afkomstig van de plastic houder van de naald. Hiervan zijn eveneens de risico's voor de gezondheid onderzocht. De aantallen deeltjes die uit naalden werden gespoeld bleken onder het niveau te zitten dat wettelijk voor injectievloeistoffen is toegestaan.

Het RIVM beveelt fabrikanten aan om zelf op een grotere schaal te onderzoeken of de (plastic) deeltjes door de injectienaalden heen kunnen komen. Daarnaast beveelt het RIVM fabrikanten aan te onderzoeken in hoeverre het gebruik van titaandioxide daadwerkelijk nodig is.

Kernwoorden: injectienaalden, epoxyhars, risicobeoordeling, BADGE, bisphenol A

[1] Volgens een klokkenluider van Terumo zou de lijm, waarmee de naald aan de plastic houder wordt vastgemaakt, niet goed zijn uitgehard en in het lichaam van de patiënt kunnen komen.

Synopsis

Injection needles
Fact finding and risk assessment of excess adhesive

Commissioned by the Dutch Health Care Inspectorate (IGZ), RIVM investigated whether excess adhesive is present in two types of injection needles from the Terumo Company (K-Pack II and Neolus).
The investigations show that less than 1 percent of the Terumo needles contain visible amounts of excess cured adhesive is found (epoxy resin). This rate is much lower than the rate of 20 percent that was mentioned in the TV program EenVandaag[2]. The RIVM also examined needles from other manufacturers. Excess cured adhesive was found in a comparably small percentage as in the Terumo needles. No completely blocked needles were found. In addition, no liquid adhesive is observed in the needles. The RIVM has investigated more than 7000 needles for this fact-finding.

Subsequently, the RIVM has assessed whether the excess adhesive poses a risk to the health of the patients under the assumption of the worst-case scenario that non-cured adhesive is administered by intravenous injection. No health effects are expected related to the evaluated components of the adhesive. For titanium dioxide (colouring agent) this could not be determined with certainty. However, based on the test results of the needles that are inspected, the probability of negative effects is considered very small. In addition, the probability of negative effects related to cured adhesive particles is considered very small.

During the investigation, plastic particles have been found in needles of various manufacturers, originating from the plastic holder of the needle. The health risks associated with this were investigated as well. The observed numbers of particles appear to be below the accepted level for solutions for injection.

The RIVM recommends manufacturers to investigate on a larger scale whether (plastic) particles can be flushed out of the injection needles. It is also recommended to investigate whether the use of titanium dioxide is actually needed as colouring agent.

Keywords: injection needles, epoxy resin, risk assessment, BADGE, bisphenol A, particles.

[2] According to the whistle-blower of Terumo the adhesive, with which the needle is attached to the plastic container, have not been well cured and may come injected to patients.

Contents

Summary

Introduction
In a broadcast of the Dutch television programme EenVandaag, a whistle-blower claimed that Terumo injection needles contain excess adhesive, presenting health risks for patients due to particles of cured adhesive or to the substances BADGE and BPA leaking from the adhesive. The Dutch Inspectorate for Health Care (IGZ) commissioned RIVM to assist in the investigation of this allegation. The RIVM investigation comprised a fact-finding phase (phase I) and a health risk assessment phase (phase II). The following research questions were composed.

Phase I
- Is excess adhesive detectable in needles from Terumo?
- Which percentage of Terumo needles is excess adhesive positive, and in which amount is excess adhesive present in these needles?
- Is excess adhesive detectable in needles from other manufacturers?

Phase II
- What is the health risk posed by the presence of excess adhesive?

According to the whistle-blower in the television broadcast, excess adhesive was present in 20% of Terumo needles. RIVM used a sample size for the investigation that would confidently detect a frequency of 5%. Sampling of needles was performed by IGZ based on this.

Results
Is excess adhesive detectable in needles from Terumo?
Microscopic inspection of 3684 Terumo needles followed by Raman spectroscopic analysis of 121 needles with visible irregularities resulted in confirmation of excess adhesive in 7 Terumo needles. Thus, excess adhesive was detected in Terumo needles, however, in a much lower frequency than suggested by EenVandaag. Neither fully blocked needles nor needles with liquid (uncured) adhesive, as shown in the documentary by EenVandaag, were observed. In some needles, particles were observed that were identified to be propylene plastic particles, originating from the manufacture of the plastic holder (hub) of the needle.

Which percentage of Terumo needles is excess adhesive positive, and in which amount is excess adhesive present in these needles?
Based on a statistical calculation, the frequency of excess adhesive positive Terumo needles can be estimated to be 0.5 %. The 95% confidence interval ranges from 0.2-1%. Therefore, we can state with 95% confidence that less than 1% of Terumo needles contain visible amounts of excess adhesive.
The observed amounts of cured excess adhesive are estimated to be below 5 nanoliter per needle.

Terumo needles flushed with water did not yield visible particles and the numbers of sub-visible particles were below the maximum acceptable levels for pharmaceutical solutions for injection. BADGE and bisphenol A (BPA) could be detected, but the amounts found after extraction were below the level of quantification. For BPA the level was not different from the background. From a risk assessment point of view BPA or BADGE levels below the LOQ have a sufficient margin of safety.

Is excess adhesive detectable in needles from other manufacturers?
Our evaluation shows that excess adhesive is also visible in injection needles from other manufacturers. Needles from 6 other manufacturers were inspected. The number and types of needles differed per manufacturer. Numbers ranged from 150 to 1140 needles per manufacturer, depending on their availability in the sample taken by IGZ. In total 3170 needles from other manufacturers were subjected to visual, microscopic inspection followed by Raman spectroscopic analysis of 78 needles with visible irregularities. In 5 needles the presence of excess adhesive was confirmed. Analysis of all needles from other manufacturers together resulted in an estimated frequency of excess adhesive positive needles of 0.5%. In some needles from the other manufacturers, plastic particles were also observed.

What is the health risk posed by the presence of excess adhesive?
The health risk associated with cured adhesive particles originating from Terumo injection needles is judged to be very low. The risk associated with plastic particles is judged to be low as well. It is recommended that manufacturers investigate on a larger sample size whether (plastic) particles can be flushed out of injection needles.

In addition, the health risk was evaluated for the chemicals present in the uncured (= liquid) adhesive. Based on the available data, the risk of adverse effects due to BPA exposure from excess adhesives in injection needles is considered negligible. No adverse effects due to BADGE exposure are expected for use of the needles. Similar conclusions were made for the other substances assessed, with the exception of TiO_2. For TiO_2 the present worst-case risk assessment for uncured (= liquid) adhesive points at a low margin of safety, meaning that a risk cannot be excluded. However, the latter risk assessment has a high level of uncertainty concerning the (unknown) systemic bioavailability of TiO_2 from cured and uncured adhesive and the lack of studies on toxicological effects of exposure to TiO_2 by relevant routes. It is recommended that manufacturers investigate the risk-benefit of using an adhesive with TiO_2.

Conclusion
Less than 1% of Terumo needles contain excess cured adhesive, in amounts that are visible through microscopic observation. Needles from other manufacturers contain excess cured adhesive in similar numbers. Plastic particles were also observed. From a risk management perspective, this should be avoided as far as possible. However, a risk assessment showed that there is no immediate health risk associated with the excess cured adhesive or the plastic particles found in these injection needles.

1 Introduction

On March 23rd, the television programme EenVandaag reported the alleged production of poor quality injection needles by Terumo Europe BV, Leuven, Belgium. In the broadcast, a whistle-blower claimed that 20% of the hypodermic needles produced by Terumo Europe in Leuven contained excess adhesive on the inside of the plastic holder (hub) and the needle. In order to assess this claim we set out to visually inspect a number of needles sufficiently large to identify the presence of excess adhesive even at a lower frequency. The investigation was to focus on needles used in the National Vaccine Program (RVP, 23-25G) and IV needles (18-21G). In addition, suspect needles of sizes indicated by the whistle-blower (27-29G) were investigated. Our approach was to visually inspect the inside of the plastic hub and the needle using a stereomicroscope. Needles with visible irregularities were further evaluated by Raman microscopy or particle counting or GC-MS analysis. This comprehensive endeavour was carried out in a very short timeframe. Therefore, most emphasis was placed on the microscopic inspection of large numbers of needles and confirmatory analysis by Raman microscopy. The flushing experiments were qualitative and indicative in nature.
The second part of the RIVM investigation concerned the assessment of the human health risks related to exposure to excess adhesive. Excess adhesive can possibly elicit two types of effects, one related to the particulate nature of a cured adhesive particle, and the other by the exposure to chemical substances from the adhesive, possibly leading to toxicity. Both types of risk are addressed separately.

2 Injection needles

IGZ submitted 185 samples from 7 different brands and different sources (Terumo, hospitals, wholesalers, pharmaceutical companies). An overview of the samples received is presented in ANNEX I. Each sample represented boxes with multiple needles of one type and batch. The submitted Terumo samples consisted of Neolus and K-pack-II type needles in a range of 18-30G. The whistle-blower provided 17 samples (all 29G) manufactured in the years 2011-2013. The sample collection provided by the whistle-blower contained 4 complaint samples and 13 samples collected from the retained samples in stock at the Terumo archive. The 4 complaint samples were not intact (e.g. cut open, needle missing) and were not included in the visual inspection.

3 Methods

3.1 Statistics

The initial report in the media mentioned that around 20% of Terumo needles have defects involving excess adhesive. For laboratory tests on Terumo needles, statistical power calculations[3] indicated that for a first-action round of testing, at least 20 out of 100 needles needed to be examined to decide on the first suspect samples. Such a number would allow (a) testing different kinds (gauges) of needles, each from (b) multiple sources with (c) a practical number of needles per sample. In a scenario where the percentage needles with excess adhesive defects would be 20%, this sample size would allow us to determine with 95% confidence that the percentage needles with excess adhesive defects would be larger than 10%. Assuming a scenario where the percentage of needles with excess adhesive defects is 5%, we would be able to determine with 95% confidence that the percentage needles with excess adhesive defects would be more than 1%. If no needles with excess adhesive defects would be found in the first round of testing, we would be able to say with 95% confidence that the percentage needles with excess adhesive defects is less than 5%.
After this first round of testing, larger numbers of Terumo needles were evaluated, to expand the number of samples tested and allow for a more reliable statistical estimate. In addition, a similar number of non-Terumo needles were examined, so the findings for Terumo needles could be compared against those for non-Terumo needles. However, as these non-Terumo needles represent needles from different manufacturers, the total number of needles for each individual manufacturer is smaller. This also applies to the number of samples or needle types per manufacturer. Consequently, it is not possible to reliably determine the percentage needles with excess adhesive defects per manufacturer, or to compare different brands.

3.2 Visual microscopic inspection

See Figure 3.2.1 for a schematic representation of an injection needle. Technicians were instructed to check (magnification at least 2.5x) for blocked needles, irregular shapes or objects in the plastic hub, and signs of excess adhesive. Most brands used a white or off-white adhesive. Terumo used an adhesive with TiO_2 as a white pigment. Therefore, excess adhesive was assumed to be present as a white substance in the area connecting the plastic hub and the needle end. Photographs provided by the whistle-blower supported this.
Two different technicians inspected every needle separately. A supervisor for a final decision inspected needles considered irregular by only one of the technicians. The supervisor forwarded the remaining irregular needles to either Raman analysis or particle counting or GC-MS analysis.

[3] For statistical calculations, we used a Poisson distribution to determine the lower and upper limit of the 95% confidence interval around the number of defective needles detected.

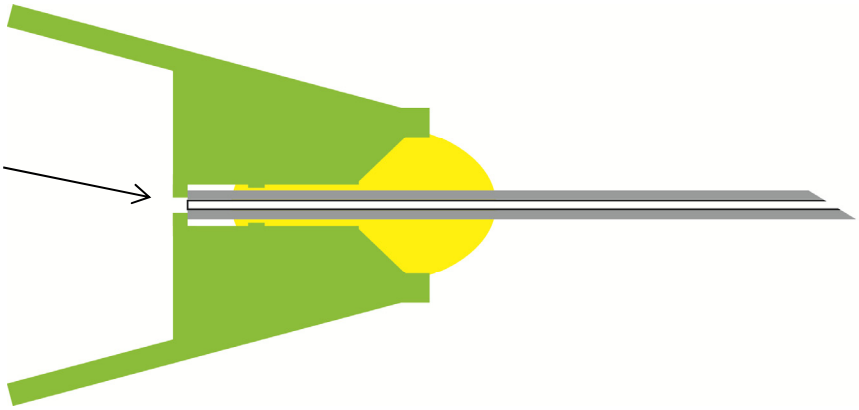

Figure 3.2.1: A cross-section of a hypodermic needle. The yellow area indicates the proper area for adhesive. The green area indicates the polypropylene hub. The arrow indicates the needle end where excess adhesive might be present.

3.3 Raman analysis

Raman microscopy was selected as the most suitable in-house technique for the confirmatory analysis of microscopic quantities of adhesive and polypropylene plastic. A specific area of interest (if any) was marked out during visual inspection.

3.3.1 Materials

Reference uncured adhesives 1-3 were provided by Henkel. Uncured adhesives 2 and 3 sampled at the Terumo production site were provided by IGZ. All other chemicals used were research grade and obtained from general suppliers.
The adhesives were cured according to the manufacturer's instructions (30 minutes in an oven equilibrated at 120^0 C).

3.3.2 Methods

Raman microscopy
Measurements were performed with a DXR Raman spectrometer fitted with a microscope (Thermo Scientific), using a 780 nm laser with a power of 14 mW, 7.5 sec. exposure time, 2 exposures, an aperture of 25 µm slit-width and a 10x or 20x objective. Before each set of measurements, the spectrometer performance was verified using a polystyrene reference standard. A region of interest was manually selected using the microscope. Needles were scored positive for excess adhesive only when a spectral contribution of BADGE or titanium dioxide was verified with a high scoring library match factor (>40%). The limit of detection was not determined.

Adhesives used by Terumo
Raman microscopy was found suitable to detect reference adhesives 1-3. No spectral differences were found for each type before and after curing. Therefore, Raman microscopy was not suited to distinguish cured from uncured (= liquid) material. Using Raman microscopy, adhesives 2 and 3, sampled at the Terumo production site could not be distinguished from the reference material.
Adhesives used by other manufacturers.

Raman microscopy was found suitable to detect the adhesives used by all other manufacturers. This was assessed by measurements of the exposed adhesive on the outside of the needle.

3.4 GC-MS Analysis

3.4.1 Materials

Bisphenol A diglycidyl ether (BADGE) was obtained from Fluka, bisphenol A (BPA) was obtained from Sigma Aldrich, for all other materials, see paragraph 3.3.

3.4.2 Methods

A Varian CP-3800 was hyphened to an Agilent technologies 240 ion trap MS and equipped with an Agilent HP-5 15 m x 0.250 mm x 0.25 mm column. A temperature gradient was employed from 100 to 280^0 C, with an injector temperature of 280^0 C and using helium as the carrier gas. Varian Workstation software was used for operation and data analysis. An analytical method was developed to identify and quantify BPA and BADGE in selected ion storage (SIS) mode using external calibration curves. Both BPA and BADGE could be determined by GC-MS with LOQ[4]s of 90 ng/mL and LOD[5]s of 20 ng/mL. From a risk assessment point of view, these LOQs are sufficiently low for 1 mL needle extracts. Blank samples showed background BPA at levels under the LOQ.

The BPA response was linear from 90 to 12500 ng/mL. The BADGE response was linear from 90 to 3125 ng/mL, and from 6250 to 50000 ng/mL. The reproducibility of the method was partially validated under the stringent timeline, and was judged adequate.

Extractions

To assess the presence of BPA and BADGE in liquid adhesive and in cured adhesive (see 3.3.1) the following experiments were conducted:

1. Liquid and cured adhesives (3 types, each 10 mg), provided by Henkel, were extracted with dichloromethane (1 mL), by gently shaking for 15 minutes at room temperature. Dichloromethane was used as a solvent because it readily dissolves BPA and BADGE. In addition, dichloromethane releases BPA or unreacted BADGE locked in the cured adhesive.

2. Liquid and cured adhesives (3 types, each 10 mg), provided by Henkel, were extracted with water (1 mL), by gently shaking for 15 minutes at room temperature. The water extracts were subsequently extracted with 1 mL of dichloromethane before introduction into the GC-MS.

To assess the presence of BPA and BADGE in Terumo needles a selection of needles was repeatedly flushed with water (5 x 1 mL). Extracts were prepared for 10 inspected Terumo needles with visible irregularities and for 10 inspected Terumo needles without visible irregularities Time constraints did not permit the analysis of more needles. The water

[4] LOQ = Limit of Quantification
[5] LOD = Limit of Detection

extracts were subsequently extracted with 1 mL of dichloromethane before introduction into the GC-MS.
As a positive control experiment, inspected needles without visible irregularities were spiked with fresh liquid adhesive A 4 µL volume of a 10 mg/mL dichloromethane solution of all three adhesives was introduced to a needle in triplicate and extracted as described above. Spiked needles were allowed to dry at room temperature for 1 hour before extraction with water as described above.

3.5 Particle Analysis

According to the European and International Standard for Sterile hypodermic needles for single use (NEN-EN-ISO 7864: 1993), the cleanliness of the needle should comply with the following:
"When inspected by normal or corrected-to-normal vision without magnification under an illuminance of 300 lx to 700 lx, the surface of the hypodermic needle tube shall appear free from particles and extraneous matter. When examined under x 2.5 magnification, the hub socket shall appear free from particles and extraneous matter".

This is consistent with the requirements for visible particles in "Parenteral Preparations – Injections" (Ph. Eur. 8.4 - 04/2015 #0520):
"*Solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles*."
Additionally, preparations for human use, solutions for infusion or solutions for injection should comply with the requirements for sub-visible particles (Ph. Eur. 8.4 – 04/2015 Chapter 2.9.19).

Since no test to investigate the potential of injection of loose particles from the inside of the needles is described in official standards, the test methods for particulate contamination of solutions for injections in the European Pharmacopoeia (Ph. Eur. 8.4 – 04/2015 Chapters 2.9.19 and 2.9.20) were used. For sub-visible particles method 1 in 2.9.19 (Light Obscuration Particle Count Test) was applied. Sample preparation as prescribed in the European Pharmacopoeia was adapted in order to fit testing injection needles as test units instead of vials with solutions for injections.

Sample preparation
Individual needles per batch were selected by visual inspection and only the insides were extracted. The needles were evaluated as small-volume parenterals with a volume of less than 25 mL. In Ph. Eur. 2.9.19, a minimum of 10 units is prescribed, unless otherwise justified and authorized. Because we did not have 10 suspected needles within 1 batch of needles from Terumo or from other brands, it was decided to test 5 suspected needles within a batch.
In Ph. Eur. 2.9.19, a minimum test volume of 25 ml is prescribed. In order to comply with this, including a small safety margin, the 5 needles were extracted with 6 ml per needle, yielding a total of 30 ml in one container. Needles were placed on a clean and sterile plastic syringe. Filtered MilliQ water (6 mL) was aspirated through the needle into the syringe and eluted into a test tube. For the 5 needles in one sample, the same syringe was used without cleaning in between.

As a control sample, an identical plastic syringe without needles was used to aspirate 6 ml five times, again leading to a total of 30 ml.

Samples were prepared by RIVM and the Laboratory of the Dutch Pharmacists (LNA, The Hague) performed particle analysis. LNA is accredited by the national accreditation body RvA. Tests on Particulate Contamination are covered by the scope (L267, dated 26-02-2014 to 01-03-2018), activity number 17 and activity number 30.

Six samples were sent to LNA:

1. Empty sampling vessel.
2. Control sample, prepared using identical syringe without needle.
3. Extract of 5 inspected Terumo needles with visible irregularities.
4. Extract of 5 inspected Terumo needles without visible irregularities.
5. Extract of 5 inspected non-Terumo needles with visible irregularities.
6. Extract of 5 inspected non-Terumo needles without visible irregularities.

4 Results of laboratory investigations

4.1 Visual inspection and Raman microscopy

In the course of the investigation, 7041 needles were inspected in duplicate. The investigated sample comprised 3181 RVP size needles (all brands, 23-25G), 2768 IV size needles (all brands, 18-21G), and 957 small-bore needles (all brands, 26-32G). Table 5.1.1 shows a summary of the inspected needles into 3 categories: needles received from the whistle-blower, Terumo needles submitted by IGZ, and other brands submitted by IGZ.

The visual inspection resulted in 621 needles with visible irregularities for further analysis. Most of these needles showed formations of what appeared to be plastic. Neither full blockages nor needles with liquid adhesive were observed. The 621 samples were distributed over Raman analysis, particle analysis, and GC-MS analysis. Raman spectroscopy was not performed on all needles, as it required partial removal of the plastic hub rendering them unsuitable for subsequent particle analysis or GC-MS.

Raman microscopy was performed on 214 needles confirming the presence of excess adhesive in 12 needles (See Figure 4.1.1 and 4.1.2). Excess adhesive was found in 7 Terumo needles and in 5 needles from other brands. In an additional 8 needles from other brands Raman microscopy found signs of excess adhesive, but the experts judged these as too weak for confirmation. Excess adhesive appeared to be firmly attached to the polypropylene or metal in all cases.

The largest drop of excess adhesive (Fig 4.1.1L, 18G needle) spanned less than 25% of the inner diameter of the needle (0.84 mm). Assuming this were a spherical droplet with a diameter of 0.21 mm this would translate into a volume of about 5 nanoliter. Most of the irregularities were formations of excess polypropylene or polypropylene particles (See Figure 4.1.3). Some of the polypropylene particles appeared to be loose.

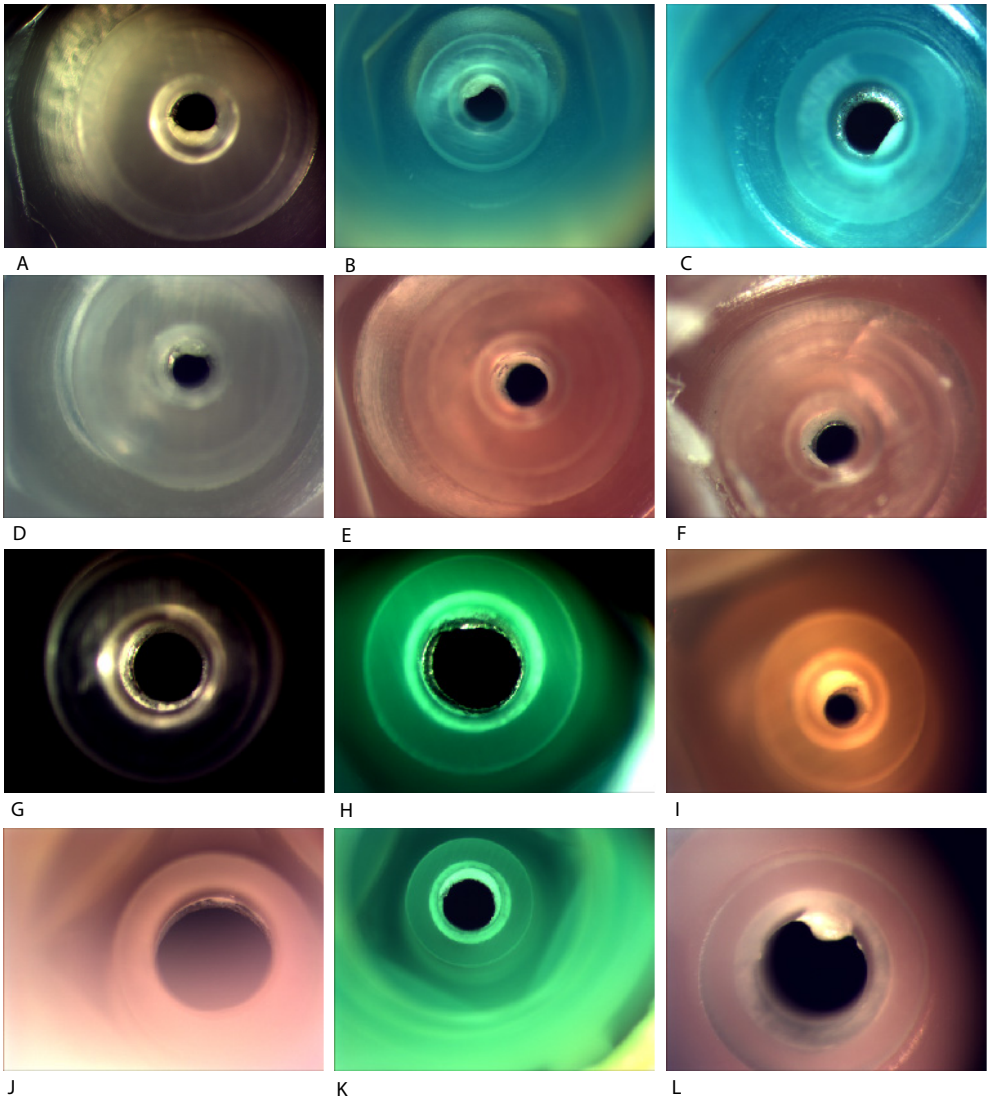

Figure 4.1.1: Photographs of needles in which excess adhesive was confirmed by Raman microscopy. Photographs were taken as visualised in Figure 3.2.1. Pictures A t/m F and H are Terumo needles.

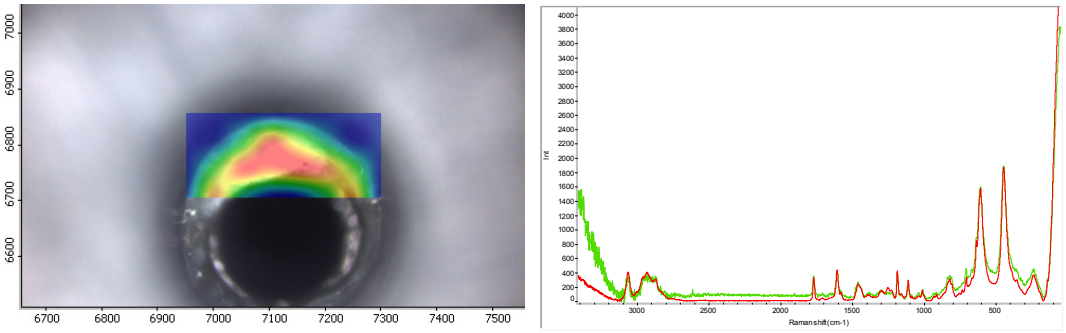

Figure 4.1.2: Raman image of excess adhesive around the needle end.
<u>Left</u>: an overlay of a correlation plot of reference resin and the excess of adhesive on a microscopic photograph of the needle as pointed out in Figure 3.2.1.
<u>Right</u>: an overlay of the Raman spectra for the needle (green) with reference adhesive obtained from Henkel (red).

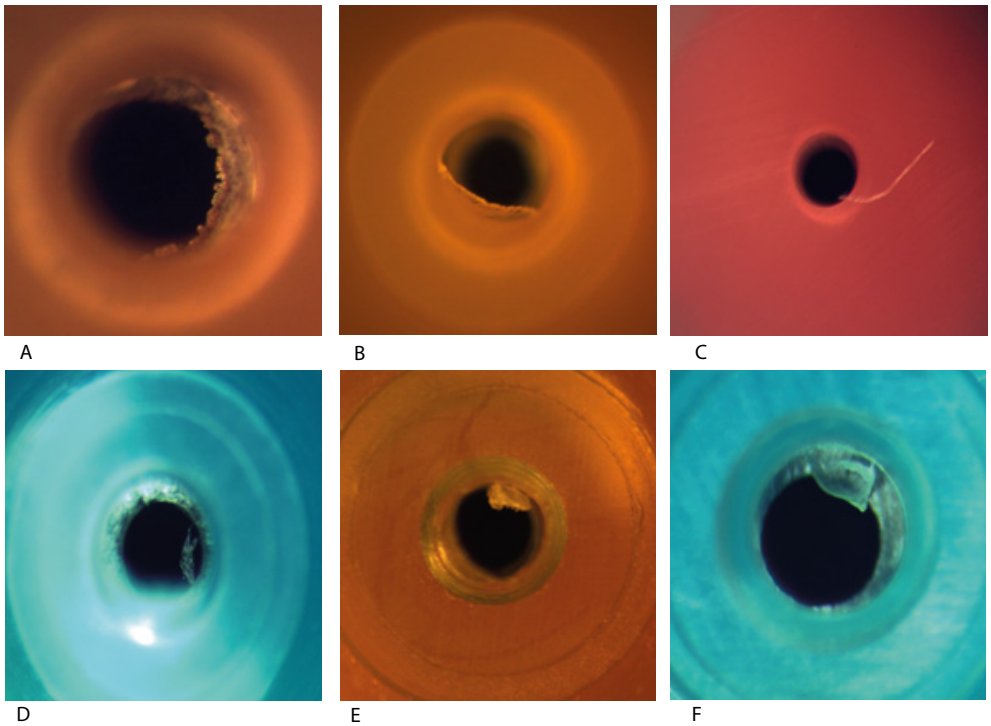

Figure 4.1.3: Example photographs of excess plastic or plastic particles near the needle end. Pictures D t/m F are Terumo needles.

4.2 GC-MS Analysis

Due to time constraints, extensive method development and sample analysis was not possible. Therefore, the focus was placed on analysis of BPA and BADGE; validation of the method was limited and only a selection of suspect needles were analysed. For the same reason, water was selected as a simulant for normal use and more lipophilic solvents or suspensions were not tested.

Extracts of adhesives provided by Henkel
High levels of BADGE were identified in all dichloromethane extracts of liquid adhesive. BADGE was also identified in dichloromethane extracts of the cured adhesive but to a much lesser extent. In all cases, the level of BPA was not different from background (< LOQ).

BADGE was identified in water extracts of liquid adhesive in a range of 4-6 µg/mL BADGE. In water extracts of the cured adhesive, BADGE was identified below the LOQ. In all cases, the level of BPA was not different from the background (< LOQ).

Extracts of Terumo needles
BADGE was detected in water extracts of Terumo needles below the LOQ in 2/10 inspected needles with visible irregularities and 1/10 inspected needles without visible irregularities. No other differences were observed. In all cases, the level of BPA was not different from the background (< LOQ).

BADGE was detected in all water extracts of spiked needles, at levels ranging from 1.5 to 7 µg/mL. The limitation of this experiment is that the retrieved quantity of BADGE exceeded its solubility in water (0.5 µg/mL). This may have to do with the crude method of introducing the adhesive into the needle. Still, the result indicates that BADGE is a suitable marker for liquid adhesive in a needle. In all cases, the level of BPA was not different from the background (< LOQ).

Due to the small sample size, the results, obtained for the detection of BADGE and BPA in the water extracts, cannot be extrapolated to injection needles in general from any manufacturer. It is recommended that manufacturers investigate on a larger sample size whether BADGE and BPA can be flushed out of injection needles.

4.3 Determination of particles

According to Ph.Eur. 2.9.19, the limits for compliance are:
Average number of particles/container ≥ 10 µm: ≤ 6000 particles
≥ 25 µm: ≤ 600 particles

Table 4.3.1: Results particulate contamination: visible and sub-visible particles

Sample	Visible particles/ white panel	Visible particles/ black panel	Sub-visible particles ≥ 10 µm	Sub-visible particles ≥ 25 µm	Test Particulate Contamination Complies **Yes/No**
2, control	0	0	1470	30	**YES**
3	0	0	930	30	**YES**
4	0	0	840	0	**YES**
5	0	**1**	930	30	**YES**
6	0	0	1020	30	**YES**

Results of the analysis for sub-visible particles showed that sub-visible particles in all 5 samples were well below the limits set by the European Pharmacopoeia. Remarkably, the test results of the flushed suspected and non-suspected needles are even lower than the control, which is obtained by sampling from identical syringes without a needle.

For the visible particle contamination only sample 5 (suspect needles from manufacturer other than Terumo) contained 1 particle. The requirements in the European Pharmacopoeia are the following: Ph.Eur. monograph #0520 requires “practically free from particles” and according to the test 2.9.20, “the presence of any particles should be recorded”.

Due to the small sample size, the results obtained for particulate contamination cannot be extrapolated to injection needles in general from any manufacturer. It is recommended that manufacturers investigate on a larger sample size whether particles can be flushed out of injection needles.

5 Conclusions laboratory investigations

5.1 Conclusion visual inspection and Raman microscopy

In the 7041 inspected needles, no full blockages were identified. Excess adhesive was confirmed in 7 Terumo needles and 5 needles from other brands. In 8 cases, there was an indication of adhesive inside the needle but this could not be confirmed with a high match factor with the spectral library. No loose particles of adhesive were observed. Needles containing liquid adhesive, as shown in the documentary by EenVandaag, were not observed. The largest volume of cured excess adhesive observed in this study was estimated to be about 5 nanoliter. Although polypropylene particles were occasionally observed, their frequency was not ascertained.

Table 5.1.1: Summary of results

Source of samples (brand)	**Visually inspected**	**Irregular**	**Raman**	**Adhesive confirmed**
Whistle-blower (Terumo)	187	53	15	0
IGZ (Terumo)	3684	297	121	7
IGZ (Other brands)	3170	271	78	5
Total	**7041**	**621**	**214**	**12**

5.2 Conclusion GC-MS

The experiments with dichloromethane have shown that cured adhesive contains a small amount of unreacted BADGE. The same experiments with water indicate that most of the unreacted BADGE is locked in the cured adhesive. Small amounts of BADGE (< LOQ) can be extracted with water from some Terumo needles. This indicates that there are no large amounts of liquid adhesive present, as shown in the documentary by EenVandaag. However, it does show that BADGE may not be fully consumed in the curing process. From a risk management perspective, incomplete curing should be avoided as far as possible.

The level of BPA was not different from the background (< LOQ) in all experiments. From a risk assessment point of view BPA or BADGE levels below the LOQ (< 90 ng IV) have a sufficient margin of safety.

Due to the small sample size, the results, obtained for the detection of BADGE and BPA in the water extracts, cannot be extrapolated to injection needles in general from any manufacturer. It is recommended that manufacturers investigate on a larger sample size whether BADGE and BPA can be flushed out of injection needles.

5.3 Conclusion particles

Results of the analysis of visible and sub-visible particles showed that sub-visible particles in all 6 samples were below the limit required by the

European Pharmacopoeia for solutions for injection. For visible particles, only the sample from suspect needles from a manufacturer other than Terumo contained 1 particle. Due to the small sample size, the results obtained for particulate contamination cannot be extrapolated to injection needles in general from any manufacturer. It is recommended that manufacturers investigate on a larger sample size whether particles can be flushed out of injection needles.

6 Risk assessment

6.1 Risks related to the injection of cured adhesive or plastic particles

Two types of risks are associated with the injection of particles: risks related to the release of residual amounts of the ingredients of the material and risks related to the particulate nature. This chapter only deals with the second type of risks i.e. the potential injection of small solid particles. Risk is a combination of the probability of occurrence of harm and the severity of that harm. Both aspects will be discussed in this chapter.

6.1.1 Probability of occurrence of injection of cured adhesive particles

The probability of occurrence of particles of cured adhesive being present at the inside of the hub or the needle, and being injected into the patient, is considered to be rare. This is because particles of epoxy resin have to originate from droplets of the viscous epoxy resin dripping into the needle hub prior to curing. A specific and limited quantity of adhesive is used in the assembly of each needle and the likelihood of it dripping beyond the needle end into the needle hub is unlikely. However, if this occurred, the drop of viscous liquid would adhere to a surface and then, on curing, would solidify. It would stick to the surface and not be free floating to be injected with the finished product. Small droplets of epoxy are not likely to be formed due to the high viscosity of the adhesive and the absence of mechanical forces during the manufacturing process that would disperse the liquid to form small droplets. It is therefore unlikely that a large number of epoxy droplets will be present in a device. The event that an adhesive particle is formed that is capable of breaking free from the device surface is considered highly unlikely, as the cured bonds are strong.

In addition, the needle assembly process at Terumo includes several quality controls at the end of the assembly process of the hub and the needle. Each unit is individually checked by camera for presence of adhesive and the quantity of adhesive on the outside, on the top of the hub. This assures that hubs with insufficient quantity of adhesive (due to insufficient application or due to loss of adhesive through the bottom of the hub), are detected and removed. In addition, another camera checks each individual unit for absence of blockages inside the needle, by assessing the amount of light that can be transmitted through the bottom of the needle-hub and can be detected at the tip of the needle. As this test may lead to false rejects if a needle is slightly off-centre, the sensitivity of the camera is that it will detect and remove needles with a blockage of 80% or more. Terumo releases only needles that pass the camera inspection. Units with partially blocked needles may still pass, if the light that is still passing through the needle is above the ejection threshold, so the controls do leave a small probability.

In addition, results of experiments on a limited number of needles showed that numbers of visible and sub-visible particles that can be

flushed out of Terumo needles were below the threshold required by the European Pharmacopoeia for solutions for injection (see paragraph 4.3).

6.1.2 Probability of occurrence of injection of plastic particles

The probability of occurrence of plastic particles being present at the inside of the hub or the needle, and being injected into the patient, is difficult to estimate. Observation of such particles was an unexpected finding while searching for excess adhesive, so they were not part of the original investigation plan. Particles found were identified as polypropylene. Their presence can be explained given the fact that the manufacture of the plastic hubs is performed by injection moulding and the plastic used is polypropylene. Depending on the process parameters, small particles can result from an injection moulding process. These parameters are unknown. The frequencies of observed plastic particles in our samples were not quantified. However, results of experiments on a limited number of needles showed that numbers of sub-visible particles that can be flushed out of Terumo needles were below the threshold required by the European Pharmacopoeia for solutions for injection (see paragraph 4.3).

6.1.3 Potential harm of injected particles

The potential harm of solid small particles originating from needles is considered to be the same as the potential harm of such particles in injectable pharmaceutical preparations. In general, injectable pharmaceutical preparations are subject to strict quality requirements. Two types of particles are being distinguished in this context: sub-visible and visible particles.

For sub-visible particles, harmonized limit values have been set in the European, Japanese and United States Pharmacopoeias: for containers smaller than 100 ml, 6000 particles ≥10 µm and 600 particles ≥ 25 µm are allowed per container when applying the preferred test method, while 3000 particles ≥10 µm and 300 particles ≥ 25 µm are allowed per container when applying the second test method (Ph. Eur. 2015a).

Visible particles are generally not acceptable. Requirements by the various pharmacopoeias are worded slightly differently, but in all cases products are expected to be "practically free" from visible particles. Inspection of 100% of all units in a batch of product is required to control this (Ph. Eur. 2015b, c; USP 2015). In cases where particles are observed in products on the market, this generally leads to recalls of the batches involved (Recall announcements). A threshold of 150 µm was proposed for human visible identification of particles in injectable drug products by Bukofzer et al., (2015), based on studies in literature that indicate that reliable detection of nearly 70% can be achieved at that limit by trained inspectors under idealized conditions. Particles of that size and somewhat larger would indeed pass injection needles used for various purposes. Terumo's product lines "Neolus" and "K-Pack II" encompasses 18 to 30 gauge (G) needle sizes that have inner diameters ranging from 0.838 mm to 0.159 mm (Wikipedia needle gauge comparison chart). Needle sizes of 18, 20 and 22 gauge are most commonly used for intravenous injection. Narrower needles are primarily used for intramuscular or subcutaneous injections.

In Recall announcements of pharmaceutical preparations due to potential presence of particles, it is indicated that intravenous administration of a solution containing sterile particulate matter may lead to adverse health consequences (Recall announcements). It is stated that the extent and severity of harm depends on the size, number, and composition of the foreign material, and the patient's underlying medical condition. Potential safety issues identified in the various recall announcements include thromboembolism, life-threatening pulmonary emboli, phlebitis, mechanical block of the capillaries or arterioles, activation of platelets or subsequent generation of micro-thrombi, localized inflammation (swelling and redness), local vein irritation, granuloma formation, allergic reactions, and systemic embolization (blockage of blood vessels, which can result in stroke, heart attack, or damage to other organs such as the kidney or liver). (Recall announcements). In some of the announcements, it is also indicated that there is no evidence indicating that intramuscular or intravenous injection of inert particles results in harm to patients when only a small amount over a limited period of time is administered or that there have been no reported adverse events for the affected lots.

A very recent review by a group of authors from the pharmaceutical industry provides an extensive overview of relevant aspects related to the topic of visible particles in injectable drug products and associated medical risks (Bukofzer et al., 2015). Their conclusion is that existing data suggest that the overall risk to patients of particle infusion is generally low.

Bukofzer et al., (2015) identify four mechanisms of potential harm, which are covering the various potential adverse effects mentioned in the recall announcements: infection and inflammation by micro-agents or endotoxins, irritating inflammation, allergic reactions and thromboembolism. They found limited data on human exposure to infused particles. Where data were available, they did relate to situations where patients were exposed to high and prolonged particle exposure. The authors’ summary on potential clinical impact is thus that particle administration has a low probability of clinically significant injury on the vascular system; reported cases are infrequent and often associated with extreme risk situations. They indicate that data suggest administration of a large volume of particles over time may cause clinical damage, while small amounts of inert particles are unlikely to cause clinically meaningful harm in patients. Furthermore, it is stated that intramuscular and subcutaneous injections of sterile, inert particles are very unlikely to cause meaningful patient injury. They do indicate that further consideration should, however, be given to patients with end-organ disease, immune-compromised, or neonates and infants, as well as when particles are injected into closed spaces (e.g., intra-thecal, intra-ocular, intra-articular) as these situations may have a greater potential for harm. It is concluded that insufficient evidence exists to conclude that intravenous injection of inert visible particles results in harm to patients (Bukofzer et al., 2015).

6.1.4 Conclusion with regard to the risk of injection of cured adhesive or plastic particles

With regard to particulate matter originating from injection needles, it can be concluded that this should be avoided as far as possible from a risk management perspective given potential adverse effects including embolism when particles are entering the blood circulation.
According to a recent review, available clinical data suggest that small amounts of inert particles are unlikely to cause clinically meaningful harm to patients.
Results of experiments on a limited number of needles showed that numbers of sub-visible particles that can be flushed out of Terumo needles were below the threshold required by the European Pharmacopoeia for solutions for injection.
The probability of occurrence of particles of cured adhesive being present at the inside of the hub or the needle, and being injected into the patient, is considered to be rare. Therefore, the health risk associated with cured adhesive particles originating from Terumo injection needles is judged to be very low.
Although only limited experimental data are available to support this, the probability of occurrence of plastic particles being present at the inside of the hub or the needle, and being injected into the patient, is considered to be small. Therefore, the risk associated with plastic particles is judged to be low. It is recommended that manufacturers investigate on a larger sample whether plastic particles can be flushed out of injection needles.

References

Bukofzer S, Ayres J, Chavez A, Devera M, Miller J, Ross D, Shabushnig J, Vargo S, Watson H, Watson R. (2015). Industry perspective on the medical risk of visible particles in injectable drug products. PDA J Pharm Sci Technol. 2015 Jan-Feb;69(1):123-39. doi: 10.5731/pdajpst.2015.01037.
Pre-press copy: http://www.pda.org/docs/default-source/website-document-library/publications/industry-perspective-on-medical-risk-of-visible-particles-in-injectable-products.pdf?sfvrsn=2

Ph. Eur. (2015a). Chapter 2.9.19 Particulate contamination: sub-visible particles. European Pharmacopoeia, 8th Ed., 2015.

Ph. Eur. (2015b). Chapter 2.9.20 Particulate contamination: visible particles. European Pharmacopoeia, 8th Ed., 2015.

Ph. Eur. (2015c). Parenteral Preparations – Injections. European Pharmacopoeia, 8th Ed., 2015. #0520.

Recall announcements
http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2011/ucm254287.htm
http://www.fda.gov/Safety/Recalls/ucm258064.htm
http://www.fda.gov/Safety/Recalls/ucm408576.htm
http://www.fda.gov/Safety/Recalls/ucm410011.htm
http://www.fda.gov/Safety/Recalls/ucm426879.htm
http://www.fda.gov/Safety/Recalls/ucm433857.htm
http://www.fda.gov/Safety/Recalls/ucm436807.htm

https://assets.digital.cabinet-office.gov.uk/media/5485ab0440f0b602440001df/con426911.pdf
https://assets.digital.cabinet-office.gov.uk/media/5485ab0740f0b602440001e3/con425135.pdf

USP 2015. Chapter 790 Visible particulates in injections. United States Pharmacopoeia 37, National Formulary 32. 2015.

Registered Nurses, 2014. http://www.registerednursern.com/iv-gauge-needles/

Wikipedia needle gauze comparison chart. http://en.wikipedia.org/wiki/Needle_gauge_comparison_chart

6.2 Toxicological risks related to the injection of adhesive

6.2.1 Method and restrictions of the performed risk evaluation

The RIVM was commissioned to provide an advice with regard to the human toxicological risks related to residues of epoxy resins used as adhesive in injection needles. Following the documentary in the television program EenVandaag and the IGZ request to the RIVM, additional information from the manufacturer of the injection needles and the manufacturer of the adhesives used was received by the RIVM. The manufacturer provided, amongst others, the components and basic formulae of the adhesives used in the production of injection needles. Because some crucial information was missing for the risk analysis, a number of assumptions needed to be made, and a worst-case approach was taken. The results are discussed, including an analysis of the assumptions and uncertainties.

Data gaps for risk assessment

The main data gaps are listed below:

- Detailed information on the composition of the cured adhesive in the injection needles as well as the migration rate of the chemicals from the uncured and cured adhesive was not available. The reactive components providing the functionality of the adhesive will have largely disappeared after the adhesive has fulfilled its purpose and has transformed into a cured film and possibly some small, cured particles.
- Detailed information on the presence of reactive components that have not reacted during the curing process of the epoxy adhesive in the injection needles.

This information is necessary for a realistic assessment of the potential harmful effects of the cured adhesive. Given that details on the composition of the cured adhesive and/or the migration of chemicals from the cured adhesive in the injection needles were lacking, the risk assessment focused on the components of the uncured adhesive.

Selection of components for risk assessment

The RIVM received the basic formulae for 3 adhesives: 'adhesive 1', 'adhesive 2'and 'adhesive 3'. From the basic formulae, 5 components were selected for risk assessment: dicyandiamine, bisphenol-A-epichlorohydrin (BADGE), phenol, silicium dioxide (SiO_2) and titanium dioxide (TiO_2). These 5 components were prioritized for risk assessment based on information on the systemic toxicity and the hazard classification (See Annex II, AII.1 for further details).

The ingredient aluminium-oxide was not selected for risk assessment even though the classification and labelling inventory (ECHA, 2015) contained some self-classifications (CLS) for Mutagenic, Carcinogenic and Reproduction toxic effects. For aluminium-oxide, the classification and labelling inventory contained over 2000 self-classifications of which 75% mentioned that a hazard classification of this substance was not warranted. A small number of the CLS (10) concerned CMR properties: Muta 2, Carc 1B and Repr. 2. We assumed that the latter classifications were based on the presence of an impurity in the aluminium-oxide. Based on the information in the classification and labelling inventory it was not possible to identify the impurity. However, the possible risk of this impurity was estimated to be low because impurities are normally present at low concentrations, the percentage of aluminium-oxide in the adhesive is low and the volume of adhesive that can be injected is limited.

The substance RP Bisphenol F-epichlorohydrin-resin MW=< 700', Cas 28064-14-4 was not selected for a risk assessment as on this substance (dimer/polymer) a limited amount of toxicological information was revealed during the selection process. The maximum content of this substance in the adhesive is 10%. This substance has a strong structural similarity with BADGE that is present in concentrations up to 50% in the adhesive. Based on time constrictions we decided not to select RP Bisphenol F-epichlorohydrin-resin for a risk assessment awaiting the results of the risk assessment on BADGE.
Seen the negligible risk due to assessed BADGE exposure we do not expect a risk for RP Bisphenol F-epichlorohydrin-resin (See Attachment 3 for further details). A risk assessment for the latter substance is not performed, as a risk due to exposure to this substance via needles is not expected. This conclusion is based on the structural similarity of both components and the fact that the concentration of RP Bisphenol F-epichlorohydrin-resin in the 3 assessed adhesives =< 10%.

Additionally, a risk assessment was performed for the substances BPA and epichlorohydrin, which are starting materials of BADGE and may be present in trace amounts in the adhesive (<10 ppm BPA according to the manufacturer).

It must be noted that degradation products of the components were not included in this risk assessment due to lack of information of their nature and/or their toxicity.

Risk assessment methodology
This advice focused on the toxicological risk related to the residues from 3 adhesives (’adhesive 1’, ’adhesive 2’or ’adhesive 3’) entering the blood circulation by taking into account all components of the uncured epoxy resin and eventual traces of BPA and epichlorohydrin (starting materials in the manufacturing process of the main ingredient).

Exposure Assessment
A worst-case exposure scenario was applied assuming persons injected themselves daily with this type of injection needle during their whole life through the intravenous (IV), intramuscular (IM) or subcutaneous (SC) route.

For systemic effects, the highest risk can be expected when residues enter the blood circulation of patients. Therefore, the IV exposure route was used for the risk assessment of systemic effects.

For local effects, IM and SC exposure routes were taken into account.

The risk assessment assessed the exposure to both children and adults. Because the incidence of injection needles containing adhesive residues is less than 1%, the exposure was considered to be intermittent.

For the amount of residual adhesive 3 exposure scenarios were considered using different amounts of residual adhesive on an injection needle:

Scenario 1:
Residual adhesive present as 1 µl, or 1.3 mg; this amount represents the volume of 3 droplets of adhesive that just fit the largest needle (18G diameter 0.838 mm).

Scenario 2:
Residual adhesive present as 100 nL, or 0.13 mg. This amount is in the same order of magnitude as the results of the University of Hasselt when they used water to extract adhesive components from contaminated needles (Carleer 2012).

Scenario 3:
Residual adhesive present as 10 nL, or 0.013 mg; this amount is in line with an estimate of the maximum size of an observed residue during the visual inspections at the RIVM (two times the estimated 5 nL, see paragraph 4.1).

Other parameters used in the exposure assessment included the density of the 3 adhesives (’adhesive 1’, ’adhesive 2’and ’adhesive 3’with densities of 1.25, 1.20 and 1.30 g/ml, respectively). A pragmatic approach was used in the exposure scenario where the highest density of 1.30 g/ml was selected for the calculations. The body weight used in the exposure scenario for adults was 70 kg body weight (bw) and 5 kg bw for children.

Regarding the potential exposure to a chemical from the adhesive, the maximum value was used as a worst-case approach. Following this assumption, exposure was considered to be 100% of the chemical present in the adhesive, as it may become directly available in the systemic circulation and because of the absence of the first pass effect (the conjugation/detoxification of chemicals that occurs in the gastrointestinal tract and the liver).

Point of departure

Toxicological information was gathered from publicly available sources. Expert toxicologists selected a point of departure (POD) from the most sensitive toxicological endpoint. An internal exposure was then derived by correcting the external No-Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) value for bioavailability.

Risk Assessment

Several risk assessment approaches were used:

1) A quantitative approach to assess systemic effects
2) A qualitative approach to assess local effects and sensitization

Systemic effects

A quantitative risk assessment was performed for systemic effects. For the risk assessment of the selected components, a margin of safety (MOS) approach was used similar to the recently published Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) Opinion on the safety of the use of Bisphenol A (BPA) in medical devices (SCENIHR 2015). In a MOS approach, the risk is evaluated by taking the ratio of the POD (NOAEL or LOAEL from a chronic study) and the estimated actual systemic exposure (internal dose). Generally, a MOS greater than 100 is considered to pose negligible risk because it takes into account inter- and intraspecies variation (uncertainty/safety) factor of 100). Given that the fraction of contaminated needles is <1%, it is justified to assess the risks based on short term or single exposure for patients receiving daily injections. For this, the European Chemicals Agency (ECHA) generally applies a factor of 3. Therefore, for the risk assessment of dicyandiamine, BADGE, SiO_2 and TiO_2, a MOS greater than 33 was considered of low concern from a public health perspective.

For phenol, because the POD was derived from a short-term study, a MOS greater than 100 was considered of low concern.

A different MOS was nevertheless used for BPA. For BPA, the European Food Safety Authority (EFSA) derived a BPA specific uncertainty/safety factor of 150 that was considered a useful safety level for continuous BPA exposure via food and for BPA exposure via medical devices (EFSA 2015, SCENIHR 2015). Based on the short term and often-single exposure in case of medical devices, the SCENIHR considers for BPA a MOS of 50 to be appropriate (EFSA 2015, SCENIHR 2015). This value was derived by the SCENIHR by dividing 150 by a factor 3, which is generally used by ECHA for extrapolation from a sub-chronic to a chronic exposure. Therefore, a MOS higher than 50 for BPA was considered to pose a negligible risk.

For components that were non-threshold carcinogens the assessed exposure level was compared with the exposure level related to an additional cancer risk of 10^{-6} for lifetime exposure. Epichlorohydrin is a known genotoxic carcinogen. After oral application to rats in drinking-water, epichlorohydrin induced tumors in the fore stomach. Based on the result of this study a risk specific dose was calculated of 0.1 µg/kg bw/day for an extra cancer risk of 10^{-6} for lifetime exposure (RIVM 2007). In this case, a MOS greater than 1 was considered to be of low concern from a public health perspective because a risk is expected when the exposure is greater than the risk specific dose (0.1 µg/kg bw/day) for an extra cancer risk of 10^{-6}.

For those components where this very worst-case approach resulted in a MOS <33 (or <50 for BPA or < 100 for phenol), an interpretation of the eventual risk and possibilities for refinement of the risk assessment were indicated.

Our conclusion with regard to the toxicological risks related to residues of epoxy resins used as adhesive in injection needles, in particular in case these residues are entering the blood circulation of patients is based on the risk assessments of the individual components.

Local effects and Sensitization
Quantitative assessment of effects after local exposure is difficult based on the available information. Therefore, a qualitative approach was applied to estimate the effects after local exposure. Local dose levels or concentrations determined local effects.

Several substances were identified in the adhesive showing effects after local exposure according to their hazard classifications. These effects include skin sensitization, irritating/corrosive effects to the skin and eyes and local effects to the lungs. For such effects, extrapolation of the

NOAELs for such effects to internal NOAELs is not possible because for some effects no NOAELs were determined and because the dose parameter was different (mg/cm^2 or mg/m^3 towards concentration in the blood or tissues). Therefore, a qualitative description of possible effects was provided.

6.2.2 Risk Assessment

Assessment of the risk due to exposure to components of uncured adhesive

Systemic effects

Following the methodology as described in section 2, the risk was assessed for 7 components of the uncured adhesive. Details of the individual assessments can be found in Annex II, AII.2 – AII.8.

Based on the worst case approach (= liquid adhesive), the risk due to single or short term exposure to the components BADGE, phenol, dicyandiamide and the eventual traces BPA and epichlorohydrin was considered to be negligible for all exposure scenarios with one exception. For the exposure of a child (5 kg b.w.) to 1 microliter of adhesive (Scenario 1), the MOS related to the exposure of BADGE was 15 and for SiO_2 26 (i.e. <33). The exposure assessment of this scenario leaves plenty of room for refinement. We consider the likelihood of this scenario as minimal, as the large size of the needles in this scenario, containing 1 microliter of adhesive will seldom be used for infants.

Based on the currently available data, a risk cannot be excluded for TiO_2. In the present assessment, a worst-case approach was taken (liquid adhesive). For the scenario in which 0.01 µL of adhesive is injected, a MOS <33 is derived for a child. This scenario was based on 100% systemic bioavailability of TiO_2 from adhesive. The reality of this scenario can still be questioned with regard to the frequency of needles from which adhesive can potentially be injected (<1%). Another main question in this assessment is if and how TiO_2 actually comes systemically available from the adhesive. Furthermore, TiO_2 may have formed complexes with adhesive components that can result in different tissue distribution and toxicity than in IV (with well-dispersed TiO2 particles) or oral studies. On the other hand, the NOAEL of 10 mg/kg bw/day (Annex II, Table AII.8.2) was based on a 30-day animal study rather than chronic exposure. Depending on the scenario, another assessment factor might be applicable. Hence, it can be concluded that a risk cannot be excluded for TiO_2 in adhesive based on the present worst-case approach, and the risk assessment needs further refinement.

Local effects - local irritation

Substances inducing local skin or eye irritation were classified based on prolonged (4 or 24 hours) exposure of skin or eyes to 100 mg per eye or

500 mg per 6 cm^2 (83 mg/ cm2) skin to the neat substance. However, after IV injection, the substance can either quickly dissolve and is diluted in the blood stream or does not quickly dissolve and will then be present in the blood stream as one or more particles. When the injected amount is limited, it is expected that the diluted substance in the blood stream will induce no or limited effects due to the low concentration of the components.

In the available *In Vitro* cytotoxicity test with an extract of 'adhesive 2' (ISO 10993-5) slight signs of reactivity (Grade 1) were observed (Toxicon confidential report). The same test using 'adhesive 3'induced no signs of reactivity (grade 0) (Toxicon confidential report). In addition to the information in the Toxicon report, the adhesive manufacturer stated that the cytotoxicity tests were performed with the cured adhesive. According to the guideline, the products are considered non-cytotoxic. This is in line with the expected low extraction rate of components from the adhesives given the limited water solubility of most of the components of the adhesives (Annex II, Table AII.9.1 and Table AII.9.2) for which information was available.

In case of IV injections, substances present as particles will circulate in the blood stream, are taken up by macrophages or get stuck in the capillaries depending on size. In the latter case, local effects at the internal surface of the blood vessel can be expected. Therefore, depending on the amount injected, a localized reaction cannot be excluded.

Due to the absence of route specific information and absence of a method for route-to-route extrapolation, it was not possible to derive NOAELs for localized effects after IV injection.

It should be noted that every IM or SC injection induces some tissue damage, including some inflammatory reaction depending on the amount and the chemicals injected.

In case of IM or SC injections, the substance can either quickly dissolve and is present at high local concentration or slowly dissolve and remain inside one or more particles. Given the expected low solubility and the negative results of the available *in vitro* cytotoxicity tests described above, local effects from dissolved substances were considered unlikely for the adhesives under consideration. Depending on size, the undissolved particles may induce a local inflammatory reaction and are taken up by macrophages or encapsulated by macrophages. Therefore, depending on the amount injected, a local reaction cannot be excluded. Due to the absence of route specific information and absence of a method for route-to-route extrapolation, it was not possible to derive NOAELs for local effects after IM and SC injection.

Sensitization

Substances classified for skin sensitization are expected to bind to proteins (hapten formation) and induce the formation of hapten-specific memory T-cells. To be able to induce T cell priming, sensitizers need to generate so-called 'danger signals' (cellular damage, oxidative stress, pro-inflammatory mediators) as well. If not, immune tolerance is induced. Upon a second exposure to the same substance, an allergic reaction will be induced clinically visible as erythema and oedema. After being sensitised the hapten-specific memory T-cells circulate through the body and allergic skin reactions can be induce via other routes of exposure as well. Most knowledge on skin sensitization is available from *in vivo* studies using dermal or intradermal exposure. The effects of exposure via IV or IM are to our knowledge not studied in great detail. However, it is known that both types of administration result in immunization. IV administration is also known to induce tolerance to some antigens.

Allergic contact dermatitis is a systemic disease that is elicited by hapten-specific memory T cells. This means that independent of the route of exposure, e.g. IM, SC or IV, allergic reactions can be elicited in sensitized individuals, if the exposure is sufficiently high and the sensitizer maintains its reactivity towards proteins during exposure. Independent of the route of exposure, the type of immune reaction is mainly a delayed-type hypersensitivity reaction (type 4) expressed as allergic contact dermatitis. This dermatitis will be systemic, i.e. at various skin sites after IV injection or locally after IM and SC injection (see Annex II, AII.10 for further details). An example is ethylene diamine, to which reactions have been described after IV exposure.

For sensitization as well as for elicitation (in already sensitized individuals) a certain amount of the sensitizing agent needs to be present. It is expected that the release of sensitizing chemicals from the adhesive is very low, which consequently makes the likelihood of sensitization or elicitation in already sensitized individuals also very low. Yet, thresholds for this condition have not been established; hence, it is not possible to do a formal quantitative risk assessment.

6.2.3 Conclusions of toxicological risk assessment

The RIVM was commissioned to provide an advice on the toxicological risk related to the residues from 3 adhesives ('adhesive 1', 'adhesive 2'and 'adhesive 3') entering the blood circulation by taking into account all components of the uncured epoxy resin and eventual traces of BPA and epichlorohydrin (starting materials in the manufacturing process of the main ingredient).

Since crucial information for the risk analysis of this case was missing, there were several uncertainties associated with this risk analysis; in

particular, the lack of information with regard to the detailed composition of the cured adhesive and the migration rate from the uncured and cured adhesive. For this reason, the risk assessment was performed for uncured adhesive. The risk analysis as performed should be interpreted as a worst-case assessment. It was assumed that all adhesive present in the needle was transferred to the body during injection. In practice, this transport may be limited because the adhesive may remain on the wall of the injection needle and the solubility of the cured adhesive or the components of the uncured adhesive might be limited in the injected liquid (most often water). The release of substances from epoxy resins is in general not instantaneous and may occur gradually during a prolonged period (Van Landuyt et al., 2011). As an example, for cured orthodontic adhesives, a continued release of BPA was noted during the 30-day observation period (Eliades et al., 2011). In absence of detailed information on the migration rate of the components, it is assumed that the systemic bioavailability of components in the adhesive is 100% after injections.

Systemic effects
For systemic effects, IV exposure was chosen as worst case. Based on the results of the worst case risk assessment of exposure to components of uncured adhesive due to single or short term exposure, it can be concluded that no adverse health effects are expected due to BPA, BADGE, dicyandiamine, epichlorohydrin, phenol or SiO_2.

For TiO_2, the present worst case risk assessment points at a low margin of safety, meaning that a risk cannot be excluded. However, the latter risk assessment has a high level of uncertainty concerning the systemic bioavailability of TiO_2 from cured and uncured adhesive and the lack of toxicological studies with a exposure route suitable for the exposure route (IV) under evaluation.

Local effects and sensitization
For local effects, intramuscular and subcutaneous exposures were considered, in addition to IV exposure. Theoretically, the local exposure to the adhesive after intramuscular or subcutaneous injections might result in localized effects, including a local inflammation, and induction or elicitation of sensitization. The occurrence of a localized reaction after injection of a residual amount of adhesive when using a contaminated needle cannot be excluded. From the present evaluation, it can be concluded that the injected amount of adhesive is too low to result in sensitization.

References
Carleer R. (2012), Onderzoek van extraheerbare lijmresten in een naald, Universiteit van Hasselt, Instituut voor materiaalonderzoek, WET/250/12/B

ECHA, classification and labelling inventory, http://echa.europa.eu/information-on-chemicals/cl-inventory-database;jsessionid=69229F9A115CDC254780A9C59D7DC646.live1 (Accessed on 16-04-2015)

EFSA (2015). Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. Part II – Toxicological assessment and risk characterisation. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), European Food Safety Authority (EFSA), Parma, Italy. EFSA Journal 13, 3978. http://www.efsa.europa.eu/en/efsajournal/doc/3978part2.pdf

Eliades T, Voutsa D, Sifakakis I, Makou M and Katsaros C (2011). Release of bisphenol-A from a light- cured adhesive bonded to lingual fixed retainers. Am J Orthod Dentofacial Orthop 139: 192-195.
MSD, MSD Risk Assessment for Terumo Needles, 10 April 2015

RIVM (2007) Environmental risk limits for twelve substances, prioritised on the basis of indicative risk limits. RIVM report 601782003/2007. http://www.rivm.nl/dsresource?objectid=rivmp:15984&type=org&disposition=inline (Accessed on 16-04-2015)

SCENIHR (2015). Scientific Committee on Emerging and Newly Identified Health Risks. Opinion on The safety of the use of bisphenol A in medical devices. European Commission, Brussels, Belgium. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_040.pdf

Van Landuyt KL, Nawrot T, Geebelen B, De Munck J, Snauwaert J, Yoshihara K, Scheers H, Godderis L, Hoet P, Van Meerbeek B. (2011). How much do resin-based dental materials release? A meta- analytical approach. Dental Materials 27, 723-747

7 Acknowledgements

We thank Prof. Dr. Ian Kimber of the University of Manchester, United Kingdom and Dr. Els Van Hoeck of the Consumer Safety – Food Contact Materials, Scientific Institute of Public Health, Brussels, Belgium for their external review and their useful comments. We thank Dr. Jan van Benthem (RIVM) and Prof. Dr. Aldert Piersma (RIVM) for critical reading.

ANNEX I: Overview of samples

Centrum Gezondheidsbescherming

Overzicht ontvangen monsters

Projectnummer : MT2015/002
Titel project : Injectienaalden Terumo
Projectnummer RIVM : V/080118/15/IN

A0790 Folder datum: 2015-03-27

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr Aantal	Toedieningsvorm	Binnenkomst
A079001	Terumo K-Pack II needle	KN-2913RB	1403028	QR code: 3941 x 5000	Injectienaald	2015-03-26
A079002	Terumo K-Pack II, needle	KN-1938RB	1411011	QR code 508 1 x 5000	Injectienaald	2015-03-26
A079003	Terumo K-Pack II, needle	KN-2525RB	1502032	QR code 189 1 x 5000	Injectienaald	2015-03-26
A079004	Terumo K-Pack II, needle	KN-3013RBKT	1411023	QR code: 9921 x 5000	Injectienaald	2015-03-26
A079005	Terumo K-Pack II, needle	KN-1838SBS	1501007	QR code 949 1 x 5000	Injectienaald	2015-03-26
A079006	Terumo K-Pack II, needle	KN-1838SB	1408029	QR code 085 1 x 5000	Injectienaald	2015-03-26
A079007	Terumo K-Pack II, needle	KN-2332RB	1410015	QR code 320 1 x 5000	Injectienaald	2015-03-26
A079008	Terumo K-Pack II, needle	KN-12325RB04	1502007	QR code 277 1 x 5000	Injectienaald	2015-03-26
A079009	Terumo K-Pack II, needle	KN-2325RB	1502035	QR code 782 1 x 5000	Injectienaald	2015-03-26
A079010	Terumo K-Pack II, needle	KN-2516RB05	1502023	QR code 641 1 x 5000	Injectienaald	2015-03-26
A079011	Terumo K-Pack II, needle	KN-2516RB04	1502020	QR code 851 1 x 5000	Injectienaald	2015-03-26
A079012	Terumo K-Pack II, needle	KN-2525RB04	1502039	QR code 668 1 x 5000	Injectienaald	2015-03-26
A079013	Terumo K-Pack II, needle	KN-2232RB	1501012	QR code 810 1 x 5000	Injectienaald	2015-03-26
A079014	Terumo K-Pack II, needle	KN-2238RB	1501013	QR code 374 1 x 5000	Injectienaald	2015-03-26
A079015	Terumo K-Pack II, needle	KN-2232RBB	1502017	QR code 636 1 x 5000	Injectienaald	2015-03-26
A079016	Terumo K-Pack II, needle	KN-2038RB	1403012	QR code 792 1 x 5000	Injectienaald	2015-03-26
A079017	Terumo K-Pack II, needle	KN-2138RB04	1411031	QR code 708 1 x 5000	Injectienaald	2015-03-26
A079018	Terumo K-Pack II, needle	KN-2138RB	1412012	QR code 245 1 x 5000	Injectienaald	2015-03-26
A079019	Terumo K-Pack II, needle	KN-2713RBKT	1501005	QR code 685 1 x 5000	Injectienaald	2015-03-26
A079020	Terumo K-Pack II, needle	KN-2713RBR	1412022	QR code 584 1 x 5000	Injectienaald	2015-03-26
A079021	Terumo K-Pack II, needle	KN-2719RB	1403013	QR code 607 1 x 5000	Injectienaald	2015-03-26
A079022	Terumo K-Pack II, needle	KN-2713RB	1502033	QR code 194 1 x 5000	Injectienaald	2015-03-26
A079023	Terumo K-Pack II, needle	KN-2719RBTS	1502019	QR code 963 1 x 5000	Injectienaald	2015-03-26

A0791 Folder datum: 2015-03-27

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr Aantal	Toedieningsvorm	Binnenkomst
A079101	LONG BEVEL	NN-2038R	1412011	QR code 686 30x 100	Injectienaald	2015-03-26
A079102	LONG BEVEL	NN-2013R	1502009	QR code 687 30 x100	Injectienaald	2015-03-26
A079103	LONG BEVEL	NN-2025R	1501018	QR code 586 30 x 100	Injectienaald	2015-03-26
A079104	SHORT BEVEL	NN-2038S	1412010	QR code 308 30 x 100	Injectienaald	2015-03-26
A079105	LONG BEVEL	NN-2050R	1408001	QR code 175 30 x 100	Injectienaald	2015-03-26
A079106	LONG BEVEL	NN-2125R	1502005	QR code 977 30 x 100	Injectienaald	2015-03-26
A079107	SHORT BEVEL	NN-2138S	1412013	QR code 696 30 x 100	Injectienaald	2015-03-26
A079108	LONG BEVEL	NN-2138R	1410002	QR code 751 30 x100	Injectienaald	2015-03-26
A079109	LONG BEVEL	NN-2132R	1402021	QR code 331 30 x100	Injectienaald	2015-03-26
A079110	LONG BEVEL	NN-2316R	1410030	QR code 996 30 x100	Injectienaald	2015-03-26
A079111	LONG BEVEL	NN-2116R	1411022	QR code 596 30 x100	Injectienaald	2015-03-26
A079112	LONG BEVEL	NN-2332R	1412005	QR code 453 30 x100	Injectienaald	2015-03-26
A079113	LONG BEVEL	NN-2325R04	1411009	QR code 751 30x 100	Injectienaald	2015-03-26
A079114	LONG BEVEL	NN-2325R	1410021	QR code 766 30 x100	Injectienaald	2015-03-26
A079115	SHORT BEVEL	NN-2332S	1405015	QR code 041 30 x100	Injectienaald	2015-03-26
A079116	LONG BEVEL	NN-2716R	1404029	QR code 260 30 x100	Injectienaald	2015-03-26
A079117	LONG BEVEL	NN-1030R	1306003	QR code 026 30 x 100	Injectienaald	2015-03-26
A079118	LONG BEVEL	NN-1938R	1406004	QR code 462 30 x100	Injectienaald	2015-03-26
A079119	SHORT BEVEL	NN-1938S	1501001	QR code 179 30 x100	Injectienaald	2015-03-26
A079120	LONG BEVEL	NN-1838R	1411016	QR code 254 30 x100	Injectienaald	2015-03-26
A079121	SHORT BEVEL	NN-1838S	1501014	QR code 610 30 x100	Injectienaald	2015-03-26
A079122	LONG BEVEL	NN-1850R	1410002	QR code977830x 100	Injectienaald	2015-03-26
A079123	LONG BEVEL	NN-2613R	1502006	QR code 583 30 x 100	Injectienaald	2015-03-26
A079124	LONG BEVEL	NN-2623R	1501012	QR code 009 30 x 100	Injectienaald	2015-03-26
A079125	LONG BEVEL	NN-2425R	1412009	QR code 846 30 x100	Injectienaald	2015-03-26

Centrum Gezondheidsbescherming

Overzicht ontvangen monsters

Projectnummer : MT2015/002
Titel project : Injectienaalden Terumo
Projectnummer RIVM : V/080118/15/IN

A079126	LONG BEVEL	NN-2232R	1410016	QR code 635	30 x 100	Injectienaald	2015-03-26
A079127	SHORT BEVEL	NN-2232S	1408018	QR code 049	30 x100	Injectienaald	2015-03-26
A079128	LONG BEVEL	NN-2232RM	1410027	QR code 251	30 x 100	Injectienaald	2015-03-26
A079129	LONG BEVEL	NN-2238R	1411020	QR code 063	30 x 100	Injectienaald	2015-03-26
A079130	LONG BEVEL	NN-2719R	1502011	QR code 273	30 x 100	Injectienaald	2015-03-26
A079131	LONG BEVEL	NN-1925R	1501005	QR code 149	30 x 100	Injectienaald	2015-03-26
A079132	LONG BEVEL	NN-2516R	1502010	QR code 871	30 x 100	Injectienaald	2015-03-26
A079133	LONG BEVEL	NN-2525R	1411013	QR code 385	30 x 100	Injectienaald	2015-03-26
A079134	LONG BEVEL	NN-1950R	1406002	QR code 538	30 x 100	Injectienaald	2015-03-26
A079135	SHORT BEVEL	NN-2070S	1501001	QR code 341	30 x 100	Injectienaald	2015-03-26
A079136	LONG BEVEL	NN-2150R	1501002	QR code 632	30 x 100	Injectienaald	2015-03-26
A079137	LONG BEVEL	NN-2250R	1411001	QR code 193	30 x 100	Injectienaald	2015-03-26
A079138	SHORT BEVEL	NN-2055S	1401001	QR code 978	30 x 100	Injectienaald	2015-03-26

A0792 Folder datum: 2015-03-27

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A079201	Injectienaald	NN-2325R04T	1502001	niet aanwezig	2x180 x5	Injectienaald	2015-03-26
A079202	Injectienaald	NN-2516R04T	1411018	niet aanwezig	2x180 x5	Injectienaald	2015-03-26

A0793 Folder datum: 2015-03-27

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A079301	K-Pack II (oranje)	KN2525RB	1406028	111747976	2 x 100	Injectienaald	2015-03-27
A079302	K-pack II (blauw)	KN2325RB	1412027	111747879	2 x 100	Injectienaald	2015-03-27
A079303	K-pack II (zalm)	2516RB05	1411018	111748073	2 x 100	Injectienaald	2015-03-27

A0794 Folder datum: 2015-03-30

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A079401	Neolus Terumo	NN-2516R	1301015	111747782	2 x 100	Injectienaald	2015-03-27
A079402	Neolus Terumo	NN-2719R	1402025	111747782	1 x 100	Injectienaald	2015-03-27
A079403	Neolus Terumo	NN-2719R	1404013	111747782	1 x 100	Injectienaald	2015-03-27
A079404	Neolus Terumo	NN-2325R	1406025	111747782	1 x 100	Injectienaald	2015-03-27
A079405	Neolus Terumo	NN-2325R	1409006	111747782	1 x 100	Injectienaald	2015-03-27

A0795 Folder datum: 2015-03-30

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A079501	Neolus Terumo	NN-1838S	1403032	111747588	2 x 100	Injectienaald	2015-03-27
A079502	Neolus Terumo	NN-1838S	1402023	111747588	2 x 100	Injectienaald	2015-03-27
A079503	Neolus Terumo	NN-2232R	1403014	111747588	2 x 100	Injectienaald	2015-03-27
A079504	Neolus Terumo	NN-2232R	1310008	111747588	2 x 100	Injectienaald	2015-03-27
A079505	Neolus Terumo	NN-1838S	1401012	111747588	2 x 100	Injectienaald	2015-03-27
A079506	Neolus Terumo	NN-2232R	1403013	111747588	2 x 100	Injectienaald	2015-03-27
A079507	Neolus Terumo	NN-2525R	1208033	111747588	2 x 100	Injectienaald	2015-03-27
A079508	Neolus Terumo	NN-1938R	13011017	111747588	2 x 100	Injectienaald	2015-03-27

A0796 Folder datum: 2015-03-30

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A079601	Terumo needle	d17	1312014	niet aanwezig	6	Injectienaald	2015-03-30
A079602	Terumo needle	d32	1312014	niet aanwezig	2	Injectienaald	2015-03-30

Centrum Gezondheidsbescherming

Overzicht ontvangen monsters

Projectnummer : MT2015/002
Titel project : Injectienaalden Terumo
Projectnummer RIVM : V/080118/15/IN

A079603	Terumo needle	KN-2913RBS	1212012	niet aanwezig	10	Injectienaald	2015-03-30
A079604	Terumo needle	PPR-13-025	1309019	niet aanwezig	2	Injectienaald	2015-03-30
A079605	Terumo needle	PPR-13-0236	niet aanwezig	niet aanwezig	1	Injectienaald	2015-03-30
A079606	Terumo needle	PPR-13-0439	1204020	niet aanwezig	1	Injectienaald	2015-03-30
A079607	Terumo needle	PPR-13-0439	1204020	niet aanwezig	34	Injectienaald	2015-03-30
A079608	Terumo needle	KN-2913RBS	1109022	niet aanwezig	11	Injectienaald	2015-03-30
A079609	Terumo needle	KN-2913RBS	1212011	niet aanwezig	19	Injectienaald	2015-03-30
A079610	Terumo needle	KN-2913RBS	1303032	niet aanwezig	20	Injectienaald	2015-03-30
A079611	Terumo needle	KN-2913RBS	1206018	niet aanwezig	19	Injectienaald	2015-03-30
A079612	Terumo needle	KN-2913RBS	1306039	niet aanwezig	19	Injectienaald	2015-03-30
A079613	Terumo needle	KN-2913RBS	1209033	niet aanwezig	9	Injectienaald	2015-03-30
A079614	Terumo needle	KN-2913RBS	1209017	niet aanwezig	19	Injectienaald	2015-03-30
A079615	Terumo needle	KN-2913RBS	1306040	niet aanwezig	10	Injectienaald	2015-03-30
A079616	Terumo needle	KN-2913RBS	1303036	niet aanwezig	9	Injectienaald	2015-03-30
A079617	Terumo needle	KN-2913RBS	1303036	niet aanwezig	1	Injectienaald	2015-03-30
A079618	info HASSELT mbt methode	niet aanwezig	niet aanwezig	niet aanwezig	1		2015-03-30

A0798 Folder datum: 2015-03-31

Order	*Productnaam*	*Nummer / code*	*Batchnr*	*Bewijkzaknr*	*Aantal*	*Toedieningsvorm*	*Binnenkomst*
A079801	Neolus	NN-2525R	1409001	111738858	1 x 100	Injectienaald	2015-03-30
A079802	Neolus	NN-2525R	1406031	111738858	1 x 100	Injectienaald	2015-03-30

A0799 Folder datum: 2015-03-31

Order	*Productnaam*	*Nummer / code*	*Batchnr*	*Bewijkzaknr*	*Aantal*	*Toedieningsvorm*	*Binnenkomst*
A079901	Neolus	NN-2150R	1412003	111738761	1 x 100	Injectienaald	2015-03-30
A079902	Neolus	NN-2325R	1410021	111738761	1 x 100	Injectienaald	2015-03-30
A079903	Neolus	NN-1850R	1109004	111738761	1 x 100	Injectienaald	2015-03-30
A079904	neolus	NN-2516R	1411012	111738761	1 x 100	Injectienaald	2015-03-30
A079905	Neolus	NN-2525R	1409001	111738761	1 x 100	Injectienaald	2015-03-30

A0800 Folder datum: 2015-03-31

Order	*Productnaam*	*Nummer / code*	*Batchnr*	*Bewijkzaknr*	*Aantal*	*Toedieningsvorm*	*Binnenkomst*
A080001	Safety Needle SOL-CARE	SN2558	13010408	111738664	1 x 100	Injectienaald	2015-03-30
A080002	Safety Needle SOL-CARE	SN2310	13010412	111738664	1 x 100	Injectienaald	2015-03-30
A080003	Safety Needle SOL-CARE	SN1810	13010424	111738664	1 x 100	Injectienaald	2015-03-30
A080004	Safety Needle SOL-CARE	SN2105	13122709	111738664	1 x 100	Injectienaald	2015-03-30

A0801 Folder datum: 2015-03-31

Order	*Productnaam*	*Nummer / code*	*Batchnr*	*Bewijkzaknr*	*Aantal*	*Toedieningsvorm*	*Binnenkomst*
A080101	BD Microlance 3	300600	150105	111734396	2 x 100	Injectienaald	2015-03-30
A080102	BD Microlance 3	300700	150213	111734396	2 x 100	Injectienaald	2015-03-30
A080103	BD Microlance 3	304432	150115	111734396	2 x 100	Injectienaald	2015-03-30
A080104	BD Microlance 3	304622	150203	111734396	2 x 100	Injectienaald	2015-03-30

A0802 Folder datum: 2015-03-31

Order	*Productnaam*	*Nummer / code*	*Batchnr*	*Bewijkzaknr*	*Aantal*	*Toedieningsvorm*	*Binnenkomst*
A080201	hypodermic needle, NIPRO	HN 1850 ET	11 K 18	111738567	1 x 100	Injectienaald	2015-03-30
A080202	hypodermic needle, NIPRO	HN 2150 ET	14 A 15	111738567	1 x 100	Injectienaald	2015-03-30

Centrum Gezondheidsbescherming

Overzicht ontvangen monsters

Projectnummer : MT2015/002
Titel project : Injectienaalden Terumo
Projectnummer RIVM : V/080118/15/IN

A080203	hypodermic needle, NIPRO	HN 2516 ET	13 A 06	111738567	1 x 100	Injectienaald	2015-03-30
A080204	hypodermic needle, NIPRO	HN 2325 ET	13 A 06	111738567	1 x 100	Injectienaald	2015-03-30

A0803 Folder datum: 2015-03-31

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A080301	SteriJect TSK hypodermic	PRE-32006	130213	111737985	1 x 100	Injectienaald	2015-03-30
A080302	SteriJect TSK hypodermic	PRE-32004	130516	111737985	1 x 100	Injectienaald	2015-03-30
A080303	SteriJect TSK hypodermic	PRE-32009	11-0606	111737985	1 x 100	Injectienaald	2015-03-30

A0804 Folder datum: 2015-03-31

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A080401	BD Microlance 3	REF 300700	150213	11738470	2 x 100	Injectienaald	2015-03-30
A080402	BD Microlance 3	REF 300600	150105	11738470	2 x 100	Injectienaald	2015-03-30
A080403	BD Microlance 3	REF 301900	141202	11738470	2 x 100	Injectienaald	2015-03-30
A080404	BD Microlance 3	REF 304434	141215	11738470	2 x 100	Injectienaald	2015-03-30

A0805 Folder datum: 2015-03-31

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A080501	Sterican	4665120	14N04G8821	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080502	Sterican	4665120	14N05G8841	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080503	Sterican	4657527	14F12G8821	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080504	Sterican	4657527	14M05G8821	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080505	Sterican	4665791	14M06G8842	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080506	Sterican	4665791	14M08G8841	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080507	Sterican	4665791	14K02G8842	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080508	Sterican	4657667	14N14G8812	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080509	Sterican	4657667	14M17G8813	niet aanwezig	2 x 100	Injectienaald	2015-03-30
A080510	Sterican	4657667	14K12G8853	niet aanwezig	2 x 100	Injectienaald	2015-03-30

A0807 Folder datum: 2015-04-01

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A080701	K-Pack II	KN-2325RB	1411020	111748849	2 x 100	Injectienaald	2015-04-01
A080702	K-Pack II	KN-2325RB	1409004	111748849	2 x 100	Injectienaald	2015-04-01
A080703	K-Pack II	KN-2516RB05	1501010	111748849	2 x 100	Injectienaald	2015-04-01

A0808 Folder datum: 2015-04-01

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A080801	Neolus	NN-2070S	1411002	111748461	2 x 100	Injectienaald	2015-04-01
A080802	Neolus	NN-2070S	1403006	111748461	38	Injectienaald	2015-04-01
A080803	Neolus	NN-2250R	1403003	111748461	55	Injectienaald	2015-04-01
A080804	Neolus	NN-2250R	1408002	111748461	1 x 100	Injectienaald	2015-04-01
A080805	Neolus	NN-2070S	1811004	111748461	17	Injectienaald	2015-04-01
A080806	Neolus	NN-2250R	0912007	111748461	5	Injectienaald	2015-04-01

A0809 Folder datum: 2015-04-01

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst

Centrum Gezondheidsbescherming

Overzicht ontvangen monsters

Projectnummer : MT2015/002
Titel project : Injectienaalden Terumo
Projectnummer RIVM : V/080118/15/IN

A080901	Neolus	NN-2070S	1407001	111748752	1x 100	Injectienaald	2015-04-01

A0810 Folder datum: 2015-04-01

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081001	Neolus	NN-2238R	1406029	111748655	2 x 100	Injectienaald	2015-04-01
A081002	Neolus	NN-2238R	1401024	111748655	2 x 100	Injectienaald	2015-04-01
A081003	Neolus	NN-2238R	1103020	111748655	2 x 100	Injectienaald	2015-04-01
A081004	Neolus	NN-2238R	1405032	111748655	x100+8	Injectienaald	2015-04-01
A081005	Neolus	NN-2238R	1311034	111748655	1x 100	Injectienaald	2015-04-01
A081006	Neolus	NN-2238R	1312009	111748655	1 x 100	Injectienaald	2015-04-01
A081007	Neolus	NN-2238R	1301046	111748655	1 x 100	Injectienaald	2015-04-01
A081008	Neolus	NN-2238R	1211017	111748655	1 x 75	Injectienaald	2015-04-01

A0811 Folder datum: 2015-04-01

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081101	Neolus	NN-2516R	1411008	111748267	1 x 100	Injectienaald	2015-04-01
A081102	Neolus	NN-2516R	1408016	111748267	1x100	Injectienaald	2015-04-01
A081103	Neolus	NN-2516R	140815	111748267	x100+6	Injectienaald	2015-04-01
A081104	Neolus	NN-2050R	1111005	111748267	2x100	Injectienaald	2015-04-01
A081105	Neolus	NN-2150R	1209004	111748170	73	Injectienaald	2015-04-01
A081106	Neolus	NN-2325R	0908024	111748170	49	Injectienaald	2015-04-01
A081107	Neolus	NN-2325R	1409006	111748170	2x100	Injectienaald	2015-04-01
A081108	Neolus	NN-2325R	1307010	111748170	2x100	Injectienaald	2015-04-01
A081109	Neolus	NN-2325R	1406025	111748170	2x100	Injectienaald	2015-04-01
A081110	Neolus	NN-1938R	1311017	111748170	90	Injectienaald	2015-04-01
A081111	Neolus	NN-2716R	1404029	111748170	2x100	Injectienaald	2015-04-01
A081112	Neolus	NN-2716R	1302023	111748170	2x100	Injectienaald	2015-04-01

A0812 Folder datum: 2015-04-01

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081201	Neolus	NN-2613R	1410009	111748364	2x100	Injectienaald	2015-04-01

A0813 Folder datum: 2015-04-02

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081301	Neolus	NN-2516R	1210041	6903085	18x5	Injectienaald	2015-04-01
A081302	Neolus	NN-2525R	1208031	6903085	17x5	Injectienaald	2015-04-01
A081303	Neolus	NN-2516R	1212014	6903085	6	Injectienaald	2015-04-01
A081304	Neolus	NN-2525R	1406005	6903085	11x5+4	Injectienaald	2015-04-01
A081305	Neolus	NN-2623R	1401009	6903085	20x5	Injectienaald	2015-04-01

A0814 Folder datum: 2015-04-02

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081401	Neolus	NN-2070S	1411002	6903084	36	Injectienaald	2015-04-01
A081402	RadioFocus Introducer	RT-R60A10PQ	1501345	6903084	1	Injectienaald	2015-04-01

Centrum Gezondheidsbescherming

Overzicht ontvangen monsters

Projectnummer : MT2015/002
Titel project : Injectienaalden Terumo
Projectnummer RIVM : V/080118/15/IN

A0815 Folder datum: 2015-04-02

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081501	Neolus	NN-2150R	1302003	111734493	51	Injectienaald	2015-04-01
A081502	Neolus	NN-2138R	1211015	111734493	14x5+1	Injectienaald	2015-04-01
A081503	Neolus	NN-2150R	1310006	111734493	100+104	Injectienaald	2015-04-01
A081504	Neolus	NN-2150R	1111002	111734493	30	Injectienaald	2015-04-01
A081505	Neolus	NN-2050R	1304007	111734493	91	Injectienaald	2015-04-01
A081506	Neolus	NN-2150R	1210007	111734493	99	Injectienaald	2015-04-01
A081507	Neolus	NN-2325R	1210030	111734493	32	Injectienaald	2015-04-01
A081508	Neolus	NN-1838R	1402003	111734493	100+97	Injectienaald	2015-04-01
A081509	Neolus	NN-2719R	1402025	111734493	28	Injectienaald	2015-04-01
A081510	Neolus	NN-2050R	1111005	111734493	44	Injectienaald	2015-04-01

A0816 Folder datum: 2015-04-02

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081601	neolus	NN-2070S	1411002	111744872	2x100	Injectienaald	2015-04-01
A081602	neolus	NN-2070S	1406003	111744872	2x100	Injectienaald	2015-04-01
A081603	neolus	NN-2516R	1408016	111744872	2x100	Injectienaald	2015-04-01
A081604	neolus	NN-2516R	1402013	111744872	2x100	Injectienaald	2015-04-01
A081605	neolus	NN-2516R	1405011	111744872	2x100	Injectienaald	2015-04-01

A0818 Folder datum: 2015-04-02

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081801	Jelco naalden	4280	2086010	niet aanwezig	200	Injectienaald	2015-04-02
A081802	Jelco naalden	41810	2353025	niet aanwezig	200	Injectienaald	2015-04-02
A081803	Jelco naalden	401815	2703791	niet aanwezig	200	Injectienaald	2015-04-02
A081804	Jelco naalden	4286	2141516	niet aanwezig	200	Injectienaald	2015-04-02
A081805	Jelco naalden	402110	2661434	niet aanwezig	200	Injectienaald	2015-04-02
A081806	Jelco naalden	402110	2675212	niet aanwezig	200	Injectienaald	2015-04-02
A081807	Jelco naalden	402310	2894510	niet aanwezig	200	Injectienaald	2015-04-02
A081808	Jelco naalden	4293	2381357	niet aanwezig	100	Injectienaald	2015-04-02
A081809	Jelco naalden	402510	2688047	niet aanwezig	200	Injectienaald	2015-04-02
A081810	Jelco naalden	402558	2555779	niet aanwezig	200	Injectienaald	2015-04-02
A081811	Jelco naalden	BN1815	130928	niet aanwezig	200	Injectienaald	2015-04-02
A081812	Jelco naalden	BN1815F	141119	niet aanwezig	200	Injectienaald	2015-04-02

A0819 Folder datum: 2015-04-07

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A081901	Neolus Terumo	NN-2070S	1411002	111737888	100	Injectienaald	2015-04-03
A081902	Neolus Terumo	NN-2250R	1408002	111737888	100	Injectienaald	2015-04-03

A0820 Folder datum: 2015-04-07

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A082001	Sterican	4665120	14N21G8841	111737791	2x100	Injectienaald	2015-04-03
A082002	Sterican	4657527	14M03G8821	111737791	2x100	Injectienaald	2015-04-03

Centrum Gezondheidsbescherming

Overzicht ontvangen monsters

Projectnummer : MT2015/002
Titel project : Injectienaalden Terumo
Projectnummer RIVM : V/080118/15/IN

A0821 Folder datum: 2015-04-07

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A082101	Terumo Injectienaalden	27 G	1403013	niet aanwezig	+/- 100	Injectienaald	2015-04-07
A082102	Terumo Injectienalden	20 G	1403012	niet aanwezig	+/- 100	Injectienaald	2015-04-07

A0823 Folder datum: 2015-04-08

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A082301	Adhesive 1	niet aanwezig	52	niet aanwezig	1		2015-04-08
A082302	Adhesive 3	niet aanwezig	77	niet aanwezig	1		2015-04-08
A082303	Adhesive 2	niet aanwezig	90	niet aanwezig	1		2015-04-08

A0826 Folder datum: 2015-04-09

Order	Productnaam	Nummer / code	Batchnr	Bewijkzaknr	Aantal	Toedieningsvorm	Binnenkomst
A082601	Neolus 21 G, goedgekeurd	niet aanwezig	1504027	niet aanwezig	5	Injectienaald	2015-04-09
A082602	Neolus 21 G, afgekeurd	niet aanwezig	1504027	niet aanwezig	5	Injectienaald	2015-04-09
A082603	K-pack 25 G, goedgekeurd	KN 25 Gx1	1504031	niet aanwezig	5	Injectienaald	2015-04-09
A082604	Staal lijm M11	Adhesive 3	33	niet aanwezig	1		2015-04-09
A082605	lijm mengvat	Adhesive 3	33	niet aanwezig	1		2015-04-09
A082606	Lijm uit blik	Adhesive 3	33	niet aanwezig	1		2015-04-09
A082607	Staal lijm M16	Adhesive 2	53	niet aanwezig	1		2015-04-09
A082608	lijm mengvat	Adhesive 2	53	niet aanwezig	1		2015-04-09
A082609	lijm uit blik	Adhesive 2	53	niet aanwezig	1		2015-04-09
A082610	k-pack II	KN 25 Gx1	1504031	niet aanwezig	5		2015-04-09

Controle

	Paraaf	Datum
Onderzoeksleider afd. KFO :		
Projectleider, afd. KFO :		30/4/2015

ANNEX II: Detailed information toxicological risk assessment

AII.1: Overview of components analysed in the toxicological risk assessment

Systemic Effects

Table AII.1.1: Overview of the components and residues selected for a quantitative risk assessment of systemic effects.

Ingredient	Maximum Concentration in adhesive (% w/w)	Classification
BADGE Cas. 25068-38-6	50	Eye Irrit. 2 Skin Irrit. 2 Skin Sens. 1
TiO_2 Cas. 13463-67-7	20	Eye Irrit. 2 STOT SE 3 STOT RE 1 Carc. 1B Skin Irrit. 2
Dicyandiamine Cas. 461-58-5	5	*Self-Classification* *Skin Irrit. 2* *Eye Irrit. 2*
SiO_2 Cas. 7631-86-9	3	*Self-Classification:* *Skin Irrit. 2* *Eye Irrit. 2* *STOT SE 2* *STOT SE 3* *STOT RE 2* *STOT RE 1* *not classified*
Phenol Cas. 108-95-2	0.5	Acute Tox. 3* Skin Corr. 1B Muta. 2 STOT RE 2* *Self-Classification* *Eye Dam. 1* *STOT RE 1* *STOT SE1*
Epichlorohydrin Cas. 68797-57-9	0.001	*Self-Classification* *Aquatic Chronic 1* *Aquatic Chronic 2* *Acute Tox. 4* *Skin Irrit. 2* *Eye Irrit. 2*
BPA Cas. 80-05-7	0.001	Repr. 2 STOT SE 3 Eye Dam. 1 Skin Sens. 1 *Self-Classification* *Aquatic Chronic 2* *Acute Tox. 4*

Local effects and Sensitization
For 8 components, we concluded based on the available toxicological information or its chemical structure that local effects (irritation, sensitization) were the main hazards. A quantitative risk assessment of these effects after injection was not possible. Therefore, a qualitative assessment of these effects was included.
Components where there was no available information
In the basic formulae, there were 10 components for which the substance identity could not be determined unequivocally or for which no toxicological information was directly available. For these components no risk assessment was performed.

AII.2: Bisphenol A (BPA)
The critical toxic effect for BPA was alteration in kidney weight in a mouse two-generation toxicity study (Tyl et al., 2008). This study was used by EFSA to derive a temporary Tolerable Daily Intake (t-TDI) for BPA via food of 4 µg/kg body weight per day (EFSA 2015). Based on the kidney toxicity a human equivalent dose (HED) of 609 µg/kg bodyweight was calculated by EFSA based on comparison of the toxicokinetics of BPA in animals and humans. However, the bioavailability in humans is limited to approximately 1% of the oral dose resulting in an internal dose of free BPA (the active toxic ingredient) of approximately 6 µg/kg bodyweight per day, which was used for the comparison with exposure to BPA present in medical devices (SCENIHR 2015). EFSA derived a BPA specific uncertainty/safety factor of 150 that was considered a useful safety level for continuous BPA exposure via food and for BPA exposure via medical devices (EFSA 2015, SCENIHR 2015). Therefore, a product is considered to pose a negligible risk if the MOS is larger than 150. SCENIHR considers a MOS of 50 to be appropriate for single use medical devices because the uncertainty factor of 150 is based on a lifelong daily exposure, in contrast to the short term and often-single exposure in the case of many medical devices. To reach this value, SCENIHR divided 150 by the common value of 3 used by ECHA for extrapolation from a sub-chronic to a chronic exposure. Although all needles contain a certain amount of adhesive, no information was available about the fraction of marketed needles containing excess adhesive that might be released. We assumed that this occurred with a very low frequency and even though patients might use injection needles on a regular basis, a MOS value of 50 or higher could be indicative of a negligible risk. This assumption should be verified when information is obtained.

Regarding the potential exposure to BPA from the adhesive, the maximum value of 10 ppm (parts per million) was used. Exposure was considered to be to 100% of the residual BPA present in the adhesive (i.e. 10 ppm according to the declaration of the manufacturer), as it may become directly available in the systemic circulation and because of

the absence of the first pass effect (the conjugation/detoxification of chemicals that occurs in the gastrointestinal tract and the liver).

Table AII.2.1: Margin of Safety analysis for BPA in adhesives used in the manufacture of injection needles.

Exposure			POD	MOS	Conclusion[†]
Scenario	Dose (mg/kg bw)[*]	Population[**]	HED internal (mg/kg bw/day)[***]		
1	0.00000019	adult	0.00609	32792	>50
	0.0000026	child	0.00609	2342	>50
2	0.00000002	adult	0.00609	327923	>50
	0.00000026	child	0.00609	23423	>50
3	0.000000002	adult	0.00609	3279231	>50
	0.000000026	child	0.00609	234231	>50

POD = Point of departure; MOS = Margin of Safety; HED = human equivalent dose
[*]Based on maximum content in adhesive of 0.001%
[**]Adult body weight 70 kg, child 5 kg
[***]Including an oral absorption of 1%
[†]Time corrected reference MOS 150/3 = 50

Conclusion

Based on the available data, the risk of adverse effects due to BPA exposure from excess adhesives in injection needles was considered to be negligible.

References

EFSA (2015). Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. Part II – Toxicological assessment and risk characterisation. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), European Food Safety Authority (EFSA), Parma, Italy. EFSA Journal 13, 3978. http://www.efsa.europa.eu/en/efsajournal/doc/3978part2.pdf

Eliades T, Voutsa D, Sifakakis I, Makou M and Katsaros C (2011). Release of bisphenol-A from a light- cured adhesive bonded to lingual fixed retainers. Am J Orthod Dentofacial Orthop 139: 192-195.

SCENIHR (2015). Scientific Committee on Emerging and Newly Identified Health Risks. Opinion on The safety of the use of bisphenol A in medical devices. European Commission, Brussels, Belgium. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_040.pdf

Tyl RW, Myers CB, Marr MC, Sloan CS, Castillo NP, Veselica MM, Seely JC, Dimond SS, Van Miller JP, Shiotsuka RN, Beyer D, Hentges SG, Waechter JM Jr. (2008). Two-generation reproductive toxicity study of dietary bisphenol A in CD-1 (Swiss) mice. Toxicol Sci. 104, 362-384.

Van Landuyt KL, Nawrot T, Geebelen B, De Munck J, Snauwaert J, Yoshihara K, Scheers H, Godderis L, Hoet P, Van Meerbeek B. (2011). How much do resin-based dental materials release? A meta- analytical approach. Dental Materials 27, 723-747.

AII.3: BADGE

Bisphenol-A-epichlorohydrin resin MW <700 is based on Bisphenol A diglycidyl ether (BADGE). BADGE is produced as a mixture of the monomer, the dimer, trimer and tetramer. BADGE is present as oligomer in commercially available liquid epoxy resins. Many of the toxicity studies were performed using this oligomeric form, whereas in some studies the pure monomer was tested. The monomer most likely is more toxic due to the presence of more active moieties in the molecule. Since the specification for the adhesive under evaluation is given as bisphenol-A-epihlorohydrin resin MW <700, the monomeric and dimeric forms will predominate (BADGE monomer has a molecular weight of 340).

The toxicity of BADGE was evaluated by EFSA (2004) in view of the use of BADGE in food can coatings. This followed earlier evaluations by the Scientific Committee for Food (SCF) from 1996, 1999 and 2002. In its evaluation, EFSA points out that BADGE is a direct-acting mutagen in *in vitro* test systems covering different genetic endpoints. In several *in vivo* studies, however, BADGE was not genotoxic (endpoints: chromosome damage in rodent bone marrow and germ cells, DNA strand breaks in liver cells). In regards to the bone marrow study, EFSA concluded that although no detectable toxic effects were seen in the target tissue, target cells most likely were exposed to the test chemical. In subsequently performed oral carcinogenicity studies with pure BADGE, no carcinogenic effect was found. Overall EFSA concluded that BADGE and its chlorohydrins do not raise concern for carcinogenicity and genotoxicity *in vivo*. The critical toxic effect identified by EFSA was increased spleen weight as seen in the chronic oral rat study. Based on an NOAEL of 15 mg/kg bw/day for this effect EFSA established a TDI of 0.15 mg/kg bw/day (EFSA 2004).

Absorption of BADGE after oral intake was described as rapid by EFSA (2004). The result of a metabolism study in which pure BADGE was dosed both orally and intravenously, indicated that 13% was absorbed after oral intake (EFSA 2004).

Pure and technical BADGE, particularly the monomer and dimer, gave positive results in Magnusson and Kligman Maximization tests in guinea pigs (EFSA 2004).
For calculating the MOS, a chronic NOAEL of 15 mg/kg bw/day, with increased spleen weight was used as critical effect. In this approach, the calculated MOS value for the highest amount of adhesive was

approximately half the reference MOS of 33 for the child, as can be seen from Table 3. This indicates a possible health risk for this group. Refinement of the assessment can demonstrate how likely an actual health risk is. Since the expected exposure is (sub)acute only, the nature of the health effects that might be expected can be explored using the available acute or sub-acute toxicity data for BADGE. The toxic effects seen in these studies may also be expected to be the first to occur when exposure via the needles is too high. No acute dose-response study was available for BADGE. As to studies with sub-acute administration, experiments with technical BADGE showed growth retardation as the only effect. This indicated that the expected adverse effect produced by (sub)acute exposure to BADGE would be relatively mild in nature.

Further, it should also be kept in mind that the exposure assessment made, using 1 µL, is a worst-case assessment for a 5 kg infant because needles of a size allowing such drop volume will seldom be used for such infants. The scenarios using the lower amounts of adhesives (0.1 and 0.01 µL) are more realistic for children.

Table AII.3.1: Margin of Safety analysis for BADGE in adhesives used in the manufacture of injection needles.

Exposure			POD	MOS	Conclusion[†]
Scenario	Dose (mg/kg bw)[*]	Population[**]	NOAEL internal (mg/kg bw/day)[***]		
1	0.00929	adult	1.95	210	>33
	0.13000	child	1.95	15	<33
2	0.00093	adult	1.95	2100	>33
	0.01300	child	1.95	150	>33
3	0.00009	adult	1.95	21000	>33
	0.00130	child	1.95	1500	>33

POD = Point of departure; MOS = Margin of Safety; NOAEL = No Observed Adverse Effect Level

[*]Based on maximum content in adhesive of 50%

[**]Adult body weight 70 kg, child 5 kg

[***]Including an oral absorption of 13%

[†]Time corrected reference MOS 100/3 = 33

Conclusion

The overall assessment is that no adverse effects due to BADGE exposure are expected for use of the needles in children or adults.

Seen the negligible risk due to BADGE exposure we do not expect a risk for RP Bisphenol F-epichlorohydrin-resin. A risk assessment for the latter substance is not performed as a risk due to exposure to this substance via needles is not expected. This conclusion is based on the structural similarity of both components and the fact that the concentration of RP Bisphenol F-epichlorohydrin-resin in the 3 assessed adhesives =< 10%.

References

EFSA (2004) Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to 2,2-bis(4-hydroxyphenyl)propane bis(2,3-epoxypropyl)ether (Bisphenol A diglycidyl ether, BADGE). *The EFSA Journal* (2004) **86**, 1-40

RIVM (1996) Bisfenol-A-diglycidyl-ether: Toxicologische beoordeling i.v.m. aanwezigheid in coatings voor voedingsmiddelen. Intern advies RIVM d.d. 29010-1996.

SCF (1996) SCF (1996) Opinion on Bisphenol A Diglycidyl Ether (Expressed on 7 june 1996). Scientific Committee for Food. Annex IV to document III/5557/96. CS/PM/2812-Final. European Commission Directorate-General III Industry.

SCF (1999) Opinion on Bisphenol A diglycidyl ether (BADGE) (expressed on 24 March 1999). SCF/CS/PM 3243 Final 6/04/99. http://ec.europa.eu/food/fs/sc/scf/out28_en.pdf (Accessed on 16-04-2015).

SCF (2002) Statement of the Scientific Committee on Food on Bisphenol A diglycidyl ether (BADGE)
(expressed on 4 December 2002). SCF/CS/PM/GEN/13510/22112002 Final 9 Dec 2002. http://ec.europa.eu/food/fs/sc/scf/out148_en.pdf (Accessed on 16-04-2015).

AII.4: Dicyandiamine

Dicyandiamine (also known as cyanoguanidine) is an odourless and colourless powder with a melting point of 209.5 °C.

The toxicity of dicyandiamine was evaluated by the OECD (2003). Further toxicological information is available from the ECHA-database. The chemical showed no reproductive or developmental toxicity in animal experiments. Several *in vitro* genotoxicity assays were negative. In chronic oral studies in rats, no carcinogenicity was found. An overall NOAEL of 15000 ppm (725 mg/kg kg bw/day) can be derived from the available toxicity data, with growth retardation as the critical effect (seen at 50,000 ppm both in the parental animals of a 2 generation rat reproduction study and in a chronic rat study) (ECHA, 2015).

No studies on the toxicokinetics of dicyandiamine were available. Based on its ready solubility in water, a relatively high absorption in the GI-tract may be assumed (50%).
Studies for dermal sensitization (Maximization test, LLNA, Draize test) for dicyandiamine were negative (ECHA, 2015).

Table AII.4.1: Margin of Safety analysis for dicyandiamine in adhesives used in the manufacture of injection needles.

Exposure			POD	MOS	Conclusion[†]
Scenario	Dose (mg/kg bw)[*]	Population[**]	NOAEL internal (mg/kg bw/day)[***]		
1	0.00093	adult	362.5	390385	>33
	0.01300	child	362.5	27885	>33
2	0.00009	adult	362.5	3903846	>33
	0.00130	child	362.5	278846	>33
3	0.00001	adult	362.5	39038462	>33
	0.00013	child	362.5	2788462	>33

POD = Point of departure; MOS = Margin of Safety; NOAEL = No Observed Adverse Effect Level

[*]Based on maximum content in adhesive of 5%

[**]Adult body weight 70 kg, child 5 kg

[***]Including an oral absorption of 50%

[†]Time corrected reference MOS 100/3 = 33

For calculating the MOS, the overall NOAEL of 725 mg/kg bw/day for growth retardation as critical effect was used. In this approach, all calculated MOS values are above the reference MOS of 33, as can be seen from Table 4, indicating absence of a health risk.

Conclusion

No health risks are expected as a result of exposure to dicyandiamine found in adhesives.

References

OECD (2003) Cyanoguanidine - CAS N°: 461-58-5. OECD SIDS. http://www.inchem.org/documents/sids/sids/461585.pdf (Accessed on 16-04-2015)

ECHA (2015) Data file on cyanoguanidine. http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7d7a63-80bd-4422-e044-00144f67d249/DISS-9c7d7a63-80bd-4422-e044-00144f67d249_DISS-9c7d7a63-80bd-4422-e044-00144f67d249.html (Accessed on 16-04-2015)

AII.5: Epichlorohydrin

Epichlorohydrin is expected to be present as impurity in the adhesive. The level at which it is present, however, is unknown. BADGE is an important component in the adhesive, which is produced using epichlorohydrin. For certain technical grades, the levels of epichlorohydrin in BADGE can be >1000 ppm. Usually levels are between 1 and 10 ppm (EFSA 2004).

Epichlorohydrin is a known genotoxic carcinogen. After oral application to rats in drinking-water, epichlorohydrin induced tumors in the forestomach. Based on the result of this study a risk specific dose was calculated of 0.1 µg/kg bw/day for an extra cancer risk of 10^{-6} for lifetime exposure (RIVM 2007).

The extra cancer risk based on 10 ppm epichlorohydrin in the adhesive was calculated assuming absorption via the oral route of 100%.

Table AII.5.1: Margin of Safety analysis for epichlorohydrin in adhesives used in the manufacture of injection needles.

Exposure			POD	MOS	Conclusion[†]
Scenario	Dose (mg/kg bw)[*]	Population[**]	Extra Cancer Risk of 10^{-6} (mg/kg bw/day)[***]		
1	0.0000002	adult	0.0001	538	>1
	0.0000026	child	0.0001	38	>1
2	0.00000002	adult	0.0001	5385	>1
	0.0000003	child	0.0001	385	>1
3	0.000000002	adult	0.0001	53846	>1
	0.00000003	child	0.0001	3846	>1

POD = Point of departure; MOS = Margin of Safety

[*]Based on maximum content in adhesive of 0.001%

[**]Adult body weight 70 kg, child 5 kg

[***]Including an oral absorption of 100%

[†]Reference MOS > 1 because a risk is expected when the exposure is greater than the risk specific dose (0.1 µg/kg bw/day) for an extra cancer risk of 10^{-6}. Exposure via the needles will occur on a very limited number occasions only; thus extra cancer per lifetime in all cases will be much below the limit for negligible risk

As illustrated in Table AII.5, in all scenarios the extra cancer risk due to exposure to the impurity epichlorohydrin is less than the exposure level related to the acceptable additional cancer risk of 10^{-6}.

Conclusion

The additional cancer risk due to the exposure as assessed in the applied worst-case scenario is negligible.

References

EFSA (2004) Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to 2,2-bis(4-

hydroxyphenyl)propane bis(2,3-epoxypropyl)ether (Bisphenol A diglycidyl ether, BADGE). The EFSA Journal (2004) 86, 1-40.

RIVM (2007) Environmental risk limits for twelve substances, prioritised on the basis of indicative risk limits. RIVM report 601782003/2007. http://www.rivm.nl/dsresource?objectid=rivmp:15984&type=org&disposition=inline (Accessed on 16-04-2015)

AII.6: Phenol

Pure phenol is a colourless or white solid. Phenol is miscible with water and is commercially sold as a liquid.

The toxicity of phenol was evaluated by the RIVM (1986, 2001, 2008). Phenol was evaluated under the EU Existing Substances Regulation, 793/93/EEC (EU RAR 2006). Further comprehensive reviews are US-EPA (2002) and ATSDR (2008).

Phenol is a strong skin irritant. Upon contact with skin, phenol causes a white wrinkly discoloration, which is not painful due to the local anaesthetizing effect by the chemical. In cosmetic practice phenol is used a skin peeling agent. These direct skin effects occur at high concentrations (more than 10%). Based on available concentration response data a NOAEC for skin irritation of 2.37% has been derived from an 18-days study in rabbits (RIVM 2008).

Toxicity studies with phenol (subacute to chronic) showed effects on liver, kidney, nervous system, immune system, blood and skin. These studies, however, were of limited quality and showed at some points contradicting results. In the EU-RAR, an overall LOAEL of 1.8 mg/kg bw/day was derived, obtained from a subacute mouse study with haematotoxicity and immunotoxicity as the critical effects. As ATSDR (2008) points out, however, the result of this study is not in line with findings in several other studies. RIVM (2001), US-EPA (2002) and ATSDR (2008) derived overall NOAELs for systemic toxicity of phenol of 40, 93 and 60 mg/kg bw/day, respectively. The value of 40 mg/kg bw/day was used for MOS evaluation. Studies on reproductive and developmental toxicity showed no adverse effect. The overall-NOAEL for reproductive and developmental toxicity was 93 mg/kg bw/day (EU-RAR 2006; RIVM 2008).

Genoxicity data for phenol showed absence of any effect in bacteria. In mammalian cells *in vitro*, however, positive effects were found for chromosomal aberrations, micronuclei, and gene mutations
In vivo, negative results were found in rodents for chromosomal aberrations, DNA strand breaks and DNA adducts. *In vivo* micronucleus tests showed negative and weakly positive results, with low frequencies of micronuclei, even at very high dose levels. Phenol is classified as a

mutagen category 2. Carcinogenicity studies do not indicate a carcinogenic action by phenol (EU-RAR 2006).

EU-RAR (2006) summarized the data on oral absorption, citing high absorption rates of ≥85% as measured in rats, sheep and pigs after oral administration. For risk assessment purposes a rate of oral absorption of 100% is recommended (EU-RAR 2006).

The available data did not show dermal sensitization by phenol (EU RAR 2006).

Table AII.6.1: Margin of Safety analysis for phenol in adhesives used in the manufacture of injection needles.

Exposure			POD	MOS	Conclusion[†]
Scenario	Dose (mg/kg bw)[*]	Population[**]	NOAEL (mg/kg bw/day)[***]		
1	0.00009	adult	40	430769	>100
	0.00130	child	40	30769	>100
2	0.00001	adult	40	4307692	>100
	0.00013	child	40	307692	>100
3	0.000001	adult	40	43076923	>100
	0.00001	child	40	3076923	>100

POD = Point of departure; MOS = Margin of Safety; NOAEL = No Observed Adverse Effect Level

[*]Based on maximum content in adhesive of 0.5%

[**]Adult body weight 70 kg, child 5 kg

[***]Including an oral absorption of 100%

[†]Reference MOS 100 (no time correction because the NOAEL was derived from a short-term developmental study)

For calculating the MOS the NOAEL of 40 mg/kg bw/day, study with haematotoxicity and immunotoxicity as the critical effects, was used. In this approach, all calculated MOS values were above the reference MOS of 100 is indicative of negligible health risk.

Conclusion

Based on the available data, the risk of exposure to phenol from adhesives is considered to be negligible.

References

ATSDR (2008) Toxicological Profile for Phenol. http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=148&tid=27 (Accessed on 16-04-2015)

EU-RAR (2006) Phenol - Summary Risk Assessment Report. Revised edition. http://echa.europa.eu/documents/10162/3e04f30d-9953-4824-ba04-defa32a130fa (Accessed on 16-04-2015)

RIVM (1986) Criteriadocument Fenol. RIVM Rapport 738513002.

RIVM (2001) Re-evaluation of human-toxicological maximum permissible risk levels. RIVM report no. 711701025. http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf (Accessed on 16-04-2015)

RIVM (2008) Advies: Fenol in kleurstoffen voor tatoeage en permanente make-up. Advies RIVM aan VWA d.d. 28-04-2008.

US-EPA (2002) Toxicological review of Phenol (CAS No. 108-95-2) In Support of Summary Information on the Integrated Risk Information System (IRIS) - September 2002. http://www.epa.gov/iris/toxreviews/0088tr.pdf (Accessed on 16-04-2015)

AII.7: Silicium dioxide

Fumed or pyrogenic amorphous silicium dioxide (SiO_2) is a commonly used material consisting of SiO_2 particles, with primary particle sizes in the nanorange (<100 nm).

SiO_2 has no harmonized classification according to the CLP Regulation (1272/2008/EC) and no self-classifications. In the REACH registrations, a Derived No Effect Level (DNEL) for long term inhalation exposure of 4 mg/m^3 was available based on irritation of the respiratory tract at the next higher dose level. This DNEL was currently not used because it was based on local effects on the lung. Oral and IV repeated dose studies with SiO_2 have recently been reviewed with a LOAEL for repeated oral dose (90-day) of 1000 mg/kg/d for a commercially available pyrogenic silica form (van Kesteren et al., 2014). At this dose, liver fibrosis was statistically significantly increased (van der Zande et al., 2014). Oral absorption of SiO_2 is dose dependent and very low (van der Zande et al., 2014; van Kesteren et al., 2014). Oral absorption for humans at the estimated dietary intake level of 9.4 mg/kg bw/day (Dekkers et al., 2011) was estimated at 0.1%. Oral absorption in the LOAEL study was estimated at 0.02% (van Kesteren et al., 2014). Once absorbed, SiO_2 mainly distributes to liver, and to a smaller extent to spleen and other tissues. The elimination half-life from liver was about a month in a kinetic study in which rats were followed up to day 90 after 5 consecutive days of IV dosing.

Some IV studies with SiO_2 were reviewed in van Kesteren et al. (2014). Ivanov et al. (2012) found liver granulomas after a single IV dose of 7 mg/kg pyrogenic silica with 60 days of follow-up. Although only one dose was applied, a considerable liver concentration was maintained throughout the 60 days due to limited elimination. This LOAEL was

therefore used for MOS evaluation, although the single dose exposure should be considered in the interpretation.

MOS values were calculated for both LOAEL values for the oral (LOAEL1 in Table AII.7.1) and IV route (LOAEL2 in Table AII.7.2). In principle, MOS values are calculated form NOAEL values. As only LOAEL values have been reported, these were presently used. This was taken into consideration in the interpretation of the calculated MOS values.
For the oral study, absorption of 0.02% was used to derive internal MOS values in which the present IV scenario for adhesive is compared to LOAEL values found in the animal studies.

Table AII.7.1: Margin of Safety analysis for SiO_2 in adhesives used in the manufacture of injection needles using a chronic LOAEL of 1000 mg/kg bw/day and an oral absorption of 0.02% (LOAEL1).

Exposure			POD	MOS	Conclusion[†]
Scenario	Dose (mg/kg bw)[*]	Population[**]	Chronic LOAEL internal (mg/kg bw/day)[***]		
1	0.00056	adult	0.2	359	>33
	0.00780	child	0.2	26	<33
2	0.00006	adult	0.2	3590	>33
	0.00078	child	0.2	256	>33
3	0.00001	adult	0.2	35897	>33
	0.00008	child	0.2	2564	>33

POD = Point of departure; MOS = Margin of Safety; LOAEL = Lowest Observed Adverse Effect Level

[*]Based on maximum content in adhesive of 3%

[**]Adult body weight 70 kg, child 5 kg

[***]Based on a chronic LOAEL of 1000 mg/kg bw/day and corrected by an oral absorption of 0.02%

[†]Time corrected reference MOS 100/3 = 33

Table AII.7.2: Margin of Safety analysis for SiO_2 in adhesives used in the manufacture of injection needles using a LOAEL of 7 mg/kg bw/day (LOAEL2).

Exposure			POD	MOS	Conclusion†
Scenario	Dose (mg/kg bw)[*]	Population[**]	LOAEL internal (mg/kg bw/day)[***]		
1	0.00056	adult	7	12564	>100
	0.00780	child	7	897	>100
2	0.00006	adult	7	125641	>100
	0.00078	child	7	8974	>100
3	0.00001	adult	7	1256410	>100
	0.00008	child	7	89744	>100

POD = Point of departure; MOS = Margin of Safety; LOAEL = Lowest Observed Adverse Effect Level

[*]Based on maximum content in adhesive of 3%

[**]Adult body weight 70 kg, child 5 kg

[***]Based on a LOAEL of 7 mg/kg bw/day

[†]Reference MOS 100 (not time corrected given single IV exposure)

Table AII.7.3: Comparison of SiO_2 exposure if all SiO_2 in adhesive becomes systemically available (100% bioavailability) to SiO_2 via external and internal exposure via the diet.

Amount of adhesive	SiO_2 exposure (mg/kg bw) via needle (=internal exposure)*	SiO_2 external exposure via diet (mg/kg/day)**	SiO_2 internal exposure via diet (mg/kg/day)***	Number of **days** of food consumption to equal internal exposure via one needle
1 µL	Adult 0.001 Child 0.008	9.4 -	0.0094 -	0.1 -
0.1 µL	Adult 0.0001 Child 0.0008	9.4 -	0.0094 -	0.01 -
0.01 µL	Adult 0.00001 Child 0.00008	9.4 -	0.0094 -	0.001 -

*Adult body weight 70 kg, child 5 kg
**Estimate for dietary intake of SiO_2 for an adult, no information available for a child
***Assuming an oral absorption of 0.1% at the dose of 9.4 mg/kg bw/d

The derived MOS values ranged between 26 and 35897 when the calculation is based on a LOAEL1 of 1000 mg/kg/d and an oral absorption of 0.02%. The MOS values ranged between 897 and over one million when the calculation was based on a LOAEL2 of 7 mg/kg for IV study. Note that in both cases LOAEL values were used rather than NOAELs. In addition, the LOAEL1, based on a 90-day study, was treated as a chronic LOAEL in this assessment. These limitations of the MOS calculation could be corrected by extrapolation from the applied test duration to chronic exposure and by extrapolation from a LOAEL to a NOAEL. However, this requires efforts beyond the scope of the current report. The very low oral absorption is a major contribution factor to the low MOS value of SiO_2.

It is assumed in the present approach that all SiO_2 present in adhesive becomes systemically available. The amount of SiO_2 in adhesive in the various scenarios is much lower than the estimated daily dietary intake that is orally absorbed (Table AII.7.3).

The main question in this assessment was whether SiO_2 actually comes systemically available from the adhesive. Furthermore, if the adhesive is injected, SiO_2 may have formed complexes with adhesive components that can result in different tissue distribution and toxicity than following IV exposure (with well-dispersed SiO_2particles) or oral studies.

Conclusion
Based on the currently available information, a risk cannot be excluded for children exposed to 1 µL. However, based on the conservative extrapolation the risk is considered unlikely. This is also in line with the minimal contribution to the daily exposure from dietary sources.

References
Dekkers, S., Krystek, P., Peters, R. J., Lankveld, D. P., Bokkers, B. G., van Hoeven-Arentzen, P. H., . . . Oomen, A. G. (2011). Presence and risks of nanosilica in food products. *Nanotoxicology, 5*(3), 393-405. doi: 10.3109/17435390.2010.519836

Ivanov, S., Zhuravsky, S., Yukina, G., Tomson, V., Korolev, D., Galagudza, M. (2012). In vivo toxicity of intravenously administered silica and silicon nanoparticles. *Materials, 5*:1873–89.

van der Zande, M., Vandebriel, R. J., Groot, M. J., Kramer, E., Herrera Rivera, Z. E., Rasmussen, K., . . . Bouwmeester, H. (2014). Sub-chronic toxicity study in rats orally exposed to nanostructured silica. *Part Fibre Toxicol, 11*(1), 8. doi: 10.1186/1743-8977-11-8

van Kesteren, P. C., Cubadda, F., Bouwmeester, H., van Eijkeren, J. C., Dekkers, S., de Jong, W. H., & Oomen, A. G. (2014). Novel insights into the risk assessment of the nanomaterial synthetic amorphous silica, additive E551, in food. *Nanotoxicology*, 1-10. doi: 10.3109/17435390.2014.940408

AII.8: Titanium dioxide
Titanium dioxide (TiO_2) is a commonly used white pigment consisting of TiO_2 particles with primary particle sizes in the range of about 60−300 nm. About 10−15% of the TiO_2 particles in white pigment are smaller than 100 nm in size (Peters et al., 2014), which corresponds to a mass fraction of TiO_2 particles smaller than 100 nm of about 0.3%.

TiO_2 as a white pigment has no harmonized classification according to the CLP Regulation (1272/2008/EC) and no self-classifications. In an oral study by the National Cancer Institute (NCI, 1979) with most probably TiO_2 as white pigment (not well characterized), no carcinogenicity was found during 103 weeks of exposure to 1250 and 2500 mg/kg bw/d (n=50/group). However, according to the non-carcinogenic effects reported in the annexes, dose-related effects were found[6]. Therefore, the LOAEL was set at 1250 mg/kg/d, which is

[6] Congestion and hemorrhage in lung of male and female rats at both doses, fibrosis in heart of male rats at both doses (increased, but no clear dose-response in female rats), hyperplasia of bile ducts in male and female rats at both doses, atrophy of the seminal vesicles and possibly testes of male rats at both doses, galactocele in mammary gland of female rats at both doses.

extrapolated to a NOAEL of 420 mg/kg bw/d by using a factor 3 (NOAEL1 in the calculations in Table AII.8.1).
In addition, oral repeated dose studies are being reviewed and point at a NOAEL of 10 mg/kg bw/d (Heringa et al., in prep). In this rat study, anatase TiO_2 with an average diameter of 75 ± 15 nm is intragastrically dosed for 30 days (Wang 2013). At a dose of 50 mg/kg/d and higher liver effects were observed (edema in young rats, infiltration of inflammatory cells in liver of adult rats, changes in liver biochemical parameters). This toxicity study was thus performed with TiO_2 particles that were generally smaller in size than TiO_2 particles as present in white pigment (NOAEL2 in the calculations in Table AII.8.2).

Oral absorption of TiO_2 was very low for several types of TiO_2 particles (Geraets et al., 2014) and was estimated at 0.02% (Heringa et al., in prep). Once absorbed, TiO_2 is mainly distributed to the liver, and to a smaller extent to the spleen, lung and other tissues. The elimination from these tissues is very slow with a relative maximum decrease for several types of TiO_2 in tissue concentration of 26% in 90 days after the last dose (Geraets et al., 2014). Based on this kinetic behaviour, accumulation of TiO_2 in time and repeated dose effects should be considered, especially in case of daily exposure such as via the diet.

MOS values were derived for both NOAEL values (Table AII.8.1 and Table AII.8.2). The oral absorption estimation of 0.02% was used to derive internal MOS values in which the present IV scenario for adhesive was compared to NOAEL values found in animal studies with oral dosing.

Table AII.8.1: Margin of Safety analysis for TiO_2 in adhesives used in the manufacture of injection needles using a NOAEL of 420 mg/kg bw/day and an oral absorption of 0.02% (NOAEL1).

Scenario	Exposure Dose (mg/kg bw)*	Population**	POD NOAEL internal (mg/kg bw/day)***	MOS	Conclusion†
1	0.00371	adult	0.084	23	<33
	0.05200	child	0.084	2	<33
2	0.00037	adult	0.084	226	>33
	0.00520	child	0.084	16	<33
3	0.00004	adult	0.084	2262	>33
	0.00052	child	0.084	162	>33

POD = Point of departure; MOS = Margin of Safety; NOAEL = No Observed Adverse Effect Level

*Based on maximum content in adhesive of 20%

**Adult body weight 70 kg, child 5 kg

***Based on a NOAEL of 420 mg/kg bw/day and corrected by an oral absorption of 0.02%

†Time corrected reference MOS 100/3 = 33

Table AII.8.2: Margin of Safety analysis for TiO_2 in adhesives used in the manufacture of injection needles using an NOAEL of 10 mg/kg bw/day (anastase TiO_2) and an oral absorption of 0.02% (NOAEL2).

Scenario	Exposure Dose (mg/kg bw)*	Population**	POD NOAEL internal (mg/kg bw/day)***	MOS	Conclusion†
1	0.00371	adult	0.002	1	<33
	0.05200	child	0.002	0.04	<33
2	0.00037	adult	0.002	5	<33
	0.00520	child	0.002	0.4	<33
3	0.00004	adult	0.002	54	>33
	0.00052	child	0.002	4	<33

POD = Point of departure; MOS = Margin of Safety; NOAEL = No Observed Adverse Effect Level

*Based on maximum content in adhesive of 20%

**Adult body weight 70 kg, child 5 kg

***Based on a NOAEL of 10 mg/kg bw/day (anastase TiO_2) and corrected by an oral absorption of 0.02%

†Time corrected reference MOS 100/3 = 33

Table AII.8.3: Comparison of TiO_2 exposure if all TiO_2 in adhesive becomes systemically available (100% bioavailability) to external and internal TiO_2 exposure via the diet.

Amount of adhesive	TiO_2 Exposure (mg/kg bw) via needle (=internal exposure)*	TiO_2 external exposure via diet (mg/kg/day)**	TiO_2 internal exposure via diet (mg/kg/day)	Number of **days** of food consumption to equal internal exposure via one needle
1 µL	Adult 0.004 Child 0.056	0.15 0.42	0.000030 0.000084	132 662
0.1 µL	Adult 0.0004 Child 0.0056	0.15 0.42	0.000030 0.000084	13 66
0.01 µL	Adult 0.00004 Child 0.00056	0.15 0.42	0.000030 0.000084	1.3 6.6

*Adult body weight 70 kg, child 5 kg
**P50 of dietary intake for adult, and P50 for child 2-6 years old

The derived MOSs were smaller or much smaller than 33 for the most worst case volumes, both for the NOAEL1 of 420 mg/kg bw/day for TiO_2 as white pigment and for the NOAEL2 of 10 mg/kg/day for repeated oral dose with TiO_2 particles of 75 ± 15 nm as currently reviewed by Heringa et al. (in prep). However, for the volume of 0.01 µL (Exposure Scenario 3), which is considered the most realistic as it is based on actual assessments, the MOS values were above the minimal MOS with the exception of one scenario for children. It should be noted that the toxicity of TiO_2 could depend on the size of the particles, where smaller sizes are generally more hazardous. The NOAEL2 is based on a 30-day study with anastase TiO_2 (i.e. small TiO_2 particles). The MOS values calculated from the NOAEL1 of 420 mg/kg bw/day were above 33 for the most realistic scenario (0.01 µL exposure).

In the present approach, it was assumed that all TiO_2 present in adhesive becomes systemically available. The internal exposure to TiO_2 from 0.1 and 0.01 µL adhesive is comparable to internal exposure from 13-66 and 1-7 days of dietary intake, respectively (Table 8c).

Also in the scenario with the smallest amount of adhesive (0.01 µL), the MOS was for some scenario's above and for others below the minimal MOS of 33 and comparison to exposure via food suggests that approximately 1 (adult) or 7 (child) days of food intake is needed to come to an similar internal exposure as from one needle (Table AII.8.3).

Geraets et al. (2014) based the estimated oral absorption of 0.02% upon studies. Literature studies can be found that suggest both higher and lower oral absorption, indicating the uncertainty of this value. Nevertheless, oral absorption in all cases is very low. The very low oral absorption is a major contribution factor to the low MOS value of TiO_2.

Conclusion

Based on the currently available data, a risk from exposure to TiO_2 cannot be excluded. In the present assessment, a worst-case approach was taken. For the most realistic scenario in which 0.01 µL of adhesive is injected, a MOS <33 was derived for a child. This scenario was based on 100% systemic bioavailability of TiO_2 from adhesive. The reality of this scenario can still be questioned with regard to the frequency of needles from which adhesive can potentially be injected (<1%). Another main question in this assessment is whether TiO_2 actually comes systemically available from the adhesive. TiO_2 may have formed complexes with adhesive components that can result in different tissue distribution and toxicity than in IV (with well-dispersed TiO2 particles) or oral studies. On the other hand, the NOAEL2 of 10 mg/kg bw/day (Table AII.8.2) is based on a 30-day animal study rather than chronic exposure. Depending on the scenario, another assessment factor may be applicable.
Hence, it can be concluded that a risk cannot be excluded for TiO_2 in adhesive based on the present worst-case approach, and the risk assessment needs further refinement.

Some IV studies with TiO_2 were available in literature, though it should be considered if these studies were performed with TiO_2 nanoparticles or TiO_2-white pigment. As a next step, assessment of the available *IV* studies may be relevant for derivation of a NOAEL based on internal exposure. In this manner, the uncertain oral absorption factor can be circumvented. Alternatively, the risk assessment can be refined with information on the properties of TiO_2 in injected adhesive, and migration of TiO_2 from injected cured and uncured adhesive.

References

Geraets, L., Oomen, A. G., Krystek, P., Jacobsen, N. R., Wallin, H., Laurentie, M., . . . de Jong, W. H. (2014). Tissue distribution and elimination after oral and intravenous administration of different titanium dioxide nanoparticles in rats. *Part Fibre Toxicol, 11*, 30. doi: 10.1186/1743-8977-11-30

National Cancer Institute (NCI) (1979) CARCINOGENESIS Technical Report Series No. 97. NCI-CG-TR-97. BIOASSAY OF TITANIUM DIOXIDE FOR POSSIBLE CARCINOGENICITY.

Peters, R. J., van Bemmel, G., Herrera-Rivera, Z., Helsper, H. P., Marvin, H. J., Weigel, S., . . . Bouwmeester, H. (2014). Characterization of Titanium Dioxide Nanoparticles in Food Products: Analytical

Methods To Define Nanoparticles. *J Agric Food Chem*. doi: 10.1021/jf5011885

Wang Y, Chen Z, Ba T, Pu J, Chen T, Song Y, Gu Y, Qian Q , Xu Y , Xiang K, Wang H , Jia G (2012) Susceptibility of young and adult rats to the oral toxicity of titanium dioxide nanoparticles. Small. doi: 10.1002/smll.201201185.

AII.9: Water Solubility of the components in the assessed adhesives

In the tables below, summarize the water solubility of the components as mentioned in the SDS for the assessed adhesives. In addition to the components mentioned in the SDS, the water solubility of TiO_2 was included.

Table AII.9.1: Water solubility of the components of 'adhesive 3'.

Substance	**CAS number**	**solubility**
Epichlorohydrin-bisphenol A resin MW <=700	25068-38-6	> 5.4 < 8.4 mg/L
CP Epichlorohydrin trimethylolpropane	30499-70-8	No information
TiO_2	13463-67-7	< 1 µg/L
SiO_2 amorphous (fumed)	7631-86-9	100 mg/L
Diethylenetriamine	111-40-0	100%

Table AII.9.2: Water solubility of the components of 'adhesive 1'and 'adhesive 2'.

Substance	**CAS number**	**solubility**
Epichlorohydrin-bisphenol A resin MW <=700	25068-38-6	> 5.4 < 8.4 mg/L
CP Epichlorohydrin trimethylolpropane	30499-70-8	No information
TiO_2	13463-67-7	< 1 µg/L
CP Phenol, FA, glycidyl ether MW<=700	28064-14-4	No information
Cashew nutshell oil epoxidized	68413-24-1	>= 0.89 <= 1.77 mg/L
CP Phenol & formaldehyde	9003-35-4	No information
Phenol	108-95-2	80 g/L

AII.10: Supplemental sensitization information

Exposure via the intradermal route is well studied, since this route is used in the Guinea Pig Maximization Test, described in OECD TG406 and ISO 10993-10 for medical device testing. Exposure via this route can lead to skin sensitization if the concentration administered is sufficiently high.

To our knowledge, there are no studies available that have investigated the effects of IV exposure to sensitizers in naïve animals. It is therefore not possible to make any conclusions on this route of exposure that are based on experimental evidence. It is only possible to predict a possible outcome, based on our knowledge on immunology. As the route of exposure, and hence the interaction with the immune system, is totally different from skin exposure, we expect that exposure may lead to immune tolerance, rather than sensitization. However, an immune response to the IV exposure to various chemicals present in the adhesive cannot be excluded.

To explain this further, it is important to consider the mechanisms involved in skin sensitization. In the skin, keratinocytes are key players in the generation of danger signals. Skin sensitizers can directly activate keratinocytes to generate these signals or keratinocytes can act as sensors of the tissue damage inflicted by the sensitizer. In the blood circulation, protein binding can occur and subsequent activation of macrophages in dendritic cells followed by T cell priming in the spleen and/or lymph nodes may be possible. Nevertheless, we expect this would lead to tolerance rather than sensitization. It is known that pharmaceuticals with sensitizing activity may in certain individuals lead to adverse immune reactions and these responses are often idiosyncratic. Hence, even if the likelihood is low, sensitization also after IV injection may potentially occur.

Exposure to sensitizers via the IM route may result in immunization (sensitization) as is clearly demonstrated by vaccination data, hence, induction of sensitization cannot be excluded.

RIVM
Committed to *health and sustainability*