Modelling local nanobiomaterial release and concentration hotspots in the environment☆

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ABSTRACT

Nanobiomaterials (NBMs) are a special category of nanomaterials used in medicine. As applications of NBMs are very similar to pharmaceuticals, their environmental release patterns are likely similar as well. Different pharmaceuticals were detected in surface waters all over the world. Consequently, there exists a need to identify possible NBM exposure routes into the environment. We estimated the local release of poly(lactic-co-glycolic acid) (PLGA), which is investigated for their use in drug delivery, to Swiss surface waters by using population data as well as type, size and location of hospitals as proxies. The total mean consumption of PLGA in Switzerland using an explorative full-market penetration scenario was calculated to be 770 kg/year. 105 hospitals were considered, which were connected to wastewater treatment plants and the receiving water body using geographic information system (GIS) modelling. The water body dataset contained 20,167 river segments and 210 lake polygons. Using the discharge of the river, we were able to calculate the PECs in different river segments. While we calculated high PLGA releases of 2.24 and 2.03 kg/year in large cities such as Geneva or Zurich, the resulting local PECs of 220 and 660 pg/l, respectively, were low due to the high river discharge (330 and 97 m³/s). High PLGA concentrations (up to 7,900 pg/l) on the other hand were calculated around smaller cities with local hospitals but also smaller receiving rivers (between 0.7 and 1.9 m³/s). Therefore, we conclude that population density does not accurately predict local concentration hotspots of NBMs, such as PLGA, that are administered in a hospital context. In addition, even at the locations with the highest predicted PLGA concentrations, the expected risk is low.

1. Introduction

Nanomaterials are defined as materials with external dimensions in the nanoscale or with an internal surface structure at the nanoscale between 1 and 100 nm (ISO, 2015). Engineered nanomaterials (ENMs) are deliberately designed and prepared materials with nanoscale dimensions (Gubala et al., 2018). Increasingly, nanomaterials are used in the medical field for the use in pharmaceutics and biomedical engineering (Küster and Adler, 2014). Nanomaterials designed to interact with the biological system for a medical purpose are termed nanobiomaterials (NBMs) (Merriam-Webster, 2020).

Only a handful of studies so far have evaluated the flows of NBMs to the environment. The flows of nano-silver (nano-Ag) used in wound dressing were estimated by Avidsson et al. (2011). Mahapatra et al. (2015) evaluated the prospective flows of nano-gold in the United States and the United Kingdom applying probabilistic material flow analysis (MFA). Hauser and Nowack (2021) applied a similar approach to model the flows of nano-Ag and poly(lactic-co-glycolic acid) (PLGA) in medical applications in Europe in 2020 assuming an explorative full-market-penetration scenario. Nano-Ag is mainly used in the medical industry due to its antibacterial, antifungal and anti-inflammatory properties (Murphy et al., 2015). While application of nano-Ag in catheters and wound dressing is already on the market, other applications such as their use in bone cement, bone tissue engineering, implant coating or dental filling is still being investigated. PLGA is a copolymer composed of lactic and glycolic acid which can easily be metabolized in the body and eliminated as water and carbon dioxide (Dinarvand et al., 2011). Thus PLGA has great potential for use as a drug delivery agent but it is

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still in the development phase and not yet available on the market. Based on the flows throughout their lifecycle, European averages of worst-case predicted environmental concentrations (wc-PECs) were calculated for different environmental and technical compartments (Hauser and Nowack, 2021).

Many more models evaluated the flows of ENMs throughout their complete lifecycle compared to NBM. These models differ in detail but also in their geographical and temporal scope (Bailleulshi et al., 2016; Williams et al., 2019). An overview of material flow models of nanomaterials from the last ten years was recently published in an article by Wigger et al. (2020). Most studies only calculated the flows and resulting predicted environmental concentrations (PECs) as country or even continent averages. However, depending on the application of the nanomaterial, regional averages can be misleading.

Many studies mention the need for the calculation of more local ENM concentrations but in reality, not many studies have done so. The study by Domercq et al. (2018) proposes a novel modelling approach for estimating exposure of ENMs in surface waters of urban environments taking into consideration spatial and temporal variability in emissions. A study by Gotschalk et al. (2011) modelled the concentration of nano-TiO$_2$, nano-ZnO and nano-Ag in Swiss rivers combining probabilistic MFA and graph theory. Highly variable local PECs were calculated with nano-TiO$_2$ having the highest concentrations ranging from 11 to 1600 ng/L. The highest concentrations were found in urban centers in the Midlands and in some tourist destinations in the Alps. Another study by Keller and Lazareva (2014) calculated environmental releases of 10 major ENMs, such as TiO$_2$, SiO$_2$, Fe$_2$O$_3$, Al$_2$O$_3$ and ZnO, in different regions of the world, different states in the United States, as well as local releases in California. Based on the flows for California, predicted concentrations in San Francisco Bay wastewater treatment plant effluent and biosolids were calculated. In some cases, the estimated local concentrations were 3–5 times greater than the concentrations estimated by other authors on a regional level. Parker and Keller (2019) predicted that the environmental concentrations are a function of the waste management practices and environmental characteristics of the location where ENMs are used and released. They conducted a case study in six watersheds for nano-TiO$_2$ using the nanoFate model. The compartment concentrations varied regionally by up to three orders of magnitude and high daily variability of nanoTiO$_2$ in air and freshwater was observed.

As NBM applications resemble those of pharmaceuticals, their release patterns are likely to be similar as well. A handful of studies estimated local concentrations of pharmaceuticals. The load of receiving pharmaceuticals into Lake Geneva of four substances (ciprofloxacin, carbamazepine, diclofenac and gabapentin) was calculated by Chêvre et al. (2013) using substance flow analysis and then compared to measured data. The modelling included hospitals and domestic use and followed the substances through wastewater treatment plants and combined sewer overflow (CSO) to the release in surface water. The predicted environmental concentrations ranged from 0.6 μg/L for carbamazepine to 2.2 μg/L for gabapentin with a residence time of 90 days. Boxall et al. (2014) used inverse modelling to estimate overall removal rates of 12 pharmaceuticals at the catchment scale in England and Wales using a hydrological model. Based on these removal rates, an exposure model across a broader landscape was developed. The calculated predicted environmental concentrations were then compared to predicted no-effect concentrations (PNECs) of the respective compounds. Lindim et al. (2017) used a fate and transport model to predict the occurrence of multiple pharmaceuticals in Swedish catchments and their drainage to the Danish Strait and the Baltic Sea. The model results showed good agreements with the monitored values. A spatially resolved model was developed by Kilgallon et al. (2017) to predict local concentrations of two pharmaceuticals (triclosan used as antimicrobial in personal care products such as toothpaste and linear alkylbenzene sulphonate used as anionic surfactant in homecare products) in Great Britain. Predicted environmental concentrations were calculated in rivers across United Kingdom counties using the Scenario assembly tool (ScrenAT). This tool uses population density and environmental parameters such as per capita water use, sewage treatment plant connectivity and dilution factor to predict local scale PECs of chemicals discharged via wastewater. The median PECs for triclosan ranged from 0.01 ng/L in western Scotland to 345 ng/L in London. For linear alkylbenzene sulphonate, the median PECs ranged from 0.03 μg/L in western Scotland to 192 μg/L in London. The PECs were compared to measured data. The modelled PECs were on average slightly higher than the mean measured data.

A very detailed local release model for micro- and macroplastic to soil, freshwater and air was developed by Kawecki and Nowack (2020). The authors used geographical datasets on land-use, population and traffic densities, locations of wastewater treatment plants (WWTPs) and combined sewer overflows as proxies, among others. High-resolution maps were generated for the release of seven commonly used polymers. The authors found that depending on the polymer, emissions were found to occur in areas with high human activities, high traffic intensity or intense agriculture. The influence of the different proxies varied for the different polymers.

NBMs have very specific applications in the treatment of very selected disease and thus local releases from specific hospitals will be very relevant. Therefore, regionally averaged releases and PECs do not accurately describe the releases of such NBMs into the environment. Many studies mentioned the need for the calculation of more local concentrations of NBMs or other chemicals compared to regional averages but only few are actually available. In this study, we developed a spatially-resolved model of the releases of NBM and identify potential hotspots of NBM releases in Switzerland and provide local PEC values. Switzerland was chosen as a case study as a previous GIS release model for plastic was available (Kawecki and Nowack, 2020) and regional mass flow models for Switzerland for several ENM have been published.

2. Methods

2.1. Adaption to the probabilistic material flow model

The probabilistic material flow model developed by Hauser and Nowack (2021) was used as the base model for the calculation of the NBM flows through technical and environmental compartments. The model describes the flows over their lifecycle for realistic and probable medical applications of nano-Ag and PLGA in Europe in one year assuming a full market-penetration of NBM-containing applications. The base model only calculates wc-PECs and does not include any fate. In our model, we also omitted transformations after the release into the environment.

Nano-Ag is used not only in medical applications but also in many consumer products (Sun et al., 2014). Modelling the local emissions of nano-Ag from medical applications would therefore not highlight hotspots of all nano-Ag releases. Therefore, we decided not to model the local releases of nano-Ag but to focus on the releases of PLGA only. Modelling the local release of PLGA can pinpoint to locations with high releases and/or high concentrations of PLGA. We considered the same PLGA applications as in the base model by Hauser and Nowack (2021). This means the improved delivery of the cancer drugs doxorubicin, paclitaxel, docetaxel and cisplatin with PLGA.

Some adjustments had to be made to the base model as it was developed for a European context and not for Switzerland. In a first step, the consumption volumes were adjusted to the Swiss market based on population (population in EU26 with United Kingdom, Switzerland & Norway: 530 million; population in Switzerland: 8.5 million (World Bank, 2020)). The adjusted consumption volumes for PLGA can be found in the Supporting Information in Table A.1.

The model uses general transfer coefficients that are independent of the NBM but dependent on the country where the study is applied. Examples of general transfer coefficients are the treatment of health care and municipal waste, sewage treatment connection rate, or cremation
rate. These general transfer coefficients were adjusted from the base model to the situation in Switzerland. The treatment options from BUWAL (2004) were used for the treatment of health care waste (also see chapter 8.2 of the Supporting Information from Hauser and Nowack (2021)). For the cremation rate, we used the value of 86.15%, which was observed in Switzerland in 2018 (The Cremation Society, 2020). For the municipal wastewater treatment, the fraction going to WWTP and on-site treatment was based on the value from OECD.Stat (2020). The ‘connection rate of population to WWTP’ was treated as connection rate to sewer system as has been done by Rajkovic et al. (2020). The connection rate in Switzerland is 98%. The values for CSOs and exfiltration were kept the same as in the base model. Just primary treatment was not assumed to occur in Switzerland, which is consistent with Rajkovic et al. (2020). All WWTPs in Switzerland use higher levels of treatment. Secondary treatment is utilized in 30% of Swiss sewage treatment plants; tertiary treatment in 70% (OECD, 2017). This 30/70-split was used for municipal sewage. However, as hospitals are not evenly distributed throughout Switzerland, their split in secondary and tertiary treatment is different. After assigning the hospitals to their respective WWTP and considering the size of the hospitals (described below), we calculated that 19% of WWTP receiving hospital sewage use secondary treatment while 81% use tertiary treatment.

Municipal solid waste (MSW) and sludge from WWTPs are completely incinerated in Switzerland (BAFU, 2019). Consequently, all MSW and sludge was modelled to flow to municipal waste incinerator plants (MWIP). Based on the application of PLGA as drug delivery agent and the fact that sewage sludge is completely incinerated in Switzerland, PLGA is only released to water. Therefore, the system boundary of our study only include the expected local releases of PLGA to water. Fig. 1 shows all the flows of the model based on Hauser and Nowack (2021), including the system boundary for this study marked in red.

The uncertainty of input parameters in the model was included by using a probability distribution for the consumption volume and transfer coefficients (Sun et al., 2014; Wang et al., 2016). Unless otherwise stated, uncertainty coefficients of ±50% were applied to all parameters. The model was run 100,000 times, each time taking a random value of the probability distribution for each parameter. The results are shown for the mean as well as the 25th and 75th quantile from the 100,000 runs.

2.2. Spatially resolved emission flows from hospitals

In a first step, the location of each hospital in Switzerland had to be defined. A list of all 281 hospitals in Switzerland was available from the Federal Office of Public Health (BAG) for the year 2018 (Bundesamt für Gesundheit, 2020). Since PLGA is used in the delivery of cancer drugs, not all types of hospitals are relevant for our study. The BAG lists 13 types of hospitals of which six were relevant for our study. These are the categories for general hospital as well as pediatrics. Other categories such as psychiatric clinics, gynecology, rehabilitation and geriatrics were excluded. This left us with a total of 105 hospitals. The size of each hospital was estimated by the number of care days. For all 105 hospitals, the geographical coordinates were determined. A map with locations of all hospitals considered in this study can be found in the Supporting Information in Figure A1.

In a next step, each hospital was assigned to their closest WWTP and CSO. The WWTP and CSO locations were taken from (FOEN, 2017). For the larger hospitals, we checked if they were assigned to the correct WWTP. If this was not the case, the connection was manually changed. WWTPs and CSOs release their water either into rivers or lakes. The model assigned the closest body of water to each WWTP and CSO. This connection was again checked manually and adjusted if necessary.

Hauser and Nowack (2021) assumed that 95% of the administered NBMs would be excreted at the hospital whereas the remaining 5% would be excreted at home. The ratio excreted at the hospitals was distributed as mentioned above. The remainder was distributed to all WWTPs in Switzerland and regionalized using the number of inhabitants connected to each WWTP. This means that WWTPs, which serve more people, receive a higher proportion of the excreted PLGA than WWTPs...
serving fewer people. The distribution to CSO was calculated in the identical manner. The same approach was used by Kawecki and Nowack (2020).

2.3. Estimation of river discharge

In order to calculate the predicted environmental concentration in different rivers segments, we need to know the discharge of the rivers. The Swiss Federal Office for the Environment (FOEN) published yearly discharge measurements from 568 locations throughout Switzerland (FOEN, 2020a). Around 200 of the measurement stations are currently active while the rest has available data from previous years. Since we are interested in the average discharge, for each station we calculated the average of all available years. In addition to the measurement stations, the FOEN modelled the discharged of some rivers with a catchment area of <3 km² based on averaged values from 1981 to 2000 (Pflaulnier and Schönenberger, 2013).

Using the modelled and measured values, a discharge was available for 2469 out of the 20,167 river segments (12%). A map with the available discharge values is available in the Supporting Information in Figure A2. Using the discharge for these river segments, the discharge for the 46 river segments with a release of more than 0.1 kg PLGA per year was estimated manually. This means, that for each of these 46 river segments, it was checked where the closest discharge value up- or downstream is available. Then inflows from smaller rivers were added or subtracted from the closest discharge value to approximate the discharge at the emission point.

2.4. Calculating the environmental concentration

In previous MFAs, the environmental concentration of a specific compartment was calculated by dividing the total flow of nanomaterials into this compartment by its volume (Sun et al., 2014). This allowed for countrywide or even continent-wide PECs. For PLGA, European worst-case predicted environmental concentrations (wc-PECs) were calculated by Hauser and Nowack (2021). The PECs are called worst-case because they represent average concentrations in well-mixed receiving compartments assuming no fate processes such as degradation or other removal processes. They represent an upper boundary of how much PLGA could end up in different environmental compartments. Since the waste treatment system in Switzerland is not equal to the average European waste and wastewater treatment system, the European wc-PECs do not accurately reflect Swiss wc-PECs. Using the Swiss compartment volumes for surface water, sediments, WWTP effluents and sludge given by Sun et al. (2014), we calculated average Swiss wc-PECs for these compartments using the expected flows from the Swiss MFA described above. For surface water, a retention time of 40 days was used following Sun et al. (2014). The average Swiss wc-PECs for surface water could then be compared to the local concentration in different river segments where emission hotspots occur.

2.5. GIS modelling

All calculations were done using R version 3.6.0 using simple features and the scripts available online. Many datasets and scripts obtained from Kawecki and Nowack (2020) could be used as a basis for our calculations. While Kawecki and Nowack (2020) calculated emissions to water and soil, we only focused on surface water as emissions to soil are not expected to occur for PLGA. The same geographical dataset used by Kawecki and Nowack (2020) on the water bodies in Switzerland was taken. The dataset contains the river network, drainage basins and lakes at a precision of 1:25,000. 20,167 river segments with an average length of 1.6 km (varying from 11 m to 18 km) and 210 polygons for the lakes are contained in the dataset (FOEN, 2020b).

The postal address for all relevant hospitals was available. Using OSM Nominatim (Open Street Map, 2021) in an R script, the postal address was translated into coordinates. The hospitals were attributed to the closest WWTP and CSO; these in turn to the closest water body (river or lake). The nearest water body was identified using the st_nearest_feature and st_distance functions in the sf package in R (Kawecki and Nowack, 2020). st_nearest_feature returns for each feature (geometry) in x the nearest feature (geometry) in set y (R-Spatial, 2021) and st_distance returns the shortest distance between two geometries (IBM, 2021). For each river segment or lake, the emissions from WWTPs and CSO were summed up to get the total emission.

For all calculations and maps, the coordinate system EPSG 2056 (CH1903 – LV95) was used. If imported data used other coordinate systems, such as CH1903 LV03, they were converted using the built-in functions in the sf package in R. For example, the coordinates for the discharge measurement stations were given as CH1903 LV03 and had to be converted. The modelled discharge could only be attributed to the stream network called GWN25-2007 (FOEN, 2021) based on “OBJECTID”. The corresponding river segment in our dataset was identified by using the function overlap.

3. Results

3.1. Probabilistic material flow model

Based on the changes of the European base model described above, the expected flows of PLGA in Switzerland as a whole were calculated. The flow diagram is shown in Fig. 2. The flows of PLGA are depicted in dark blue. If the PLGA is transformed, the flow is shown in gray. The arrow thickness is proportional to the material input into the system. An explorative full market-penetration scenario was used, assuming that all realistic and probable applications using PLGA would reach 100% market share within their product group. Therefore, the calculated consumption value is an upper boundary of how much PLGA could be consumed annually in Switzerland in the near future. Using this scenario, a mean total of 770 kg of PLGA is predicted to be consumed annually in Switzerland. In comparison to other ENMs, this value is rather low. For example, Sun et al. (2014) estimated the annual production volume of fullerenes in Switzerland at 610 kg, nano-Ag at 1120 kg, carbon nanotubes (CNT) at 12,700 kg and nano-TiO₂ at even 337,000 kg. As sewage sludge is incinerated completely, no release of PLGA to soil is expected in Switzerland. The majority (96%) of PLGA is transformed throughout the life cycle. The only releases of PLGA to the environment occur to surface and subsurface water. The mean total annual releases to surface water are 28 kg (Q25: 12 kg; Q75: 33 kg), those to subsurface water 9.7 kg (6.5 kg; 15 kg). 3% of the total consumption ends up in surface water, 1% in subsurface water. The distribution to different environmental compartments can be found in the Supporting Information in Figure A3.

3.2. Spatially resolved emission flows

The total mass of 28 kg emitted to surface waters was then distributed geographically. In total, 2324 emission points were calculated throughout Switzerland. An emission point is either a river segment or lake into which PLGA is released. Lakes account for 45 of the emission points, rivers the other 2279. As mentioned before, only 105 hospitals were considered. Hauser and Nowack (2021) assumed that the PLGA was administered intravenously in the hospital. 95% of the excreted PLGA was assumed be excreted at the hospital, the remaining 5% at home. The releases of these 5% were distributed throughout Switzerland based on population density.

The highest emission point was found to be southwest of the city of Geneva into the river Rhone with a release of 2.24 kg of PLGA per year. West of Zurich a release of 2.03 kg/year was calculated into the river Limmat. These points are marked with a large circle in dark-red in Fig. 3. At six other locations releases between 1 and 2 kg/year were calculated. These releases occur into the rivers Ticino close to Bellinzona in
Fig. 2. Flow diagram for PLGA in Switzerland (flows in kg) assuming an explorative full-market penetration for all realistic and probable applications using PLGA in a medical context. Bold: mean of flow; in parentheses: Q25; Q75. WWTP: Wastewater treatment plant, MWIP: municipal waste incinerator plant, HWIP: hazardous waste incinerator plant. All the values are extracted from probability distributions and are rounded to two significant numbers; therefore the balance between input and output flows from one compartment might not be 100% closed.

Fig. 3. Location of emission points with releases higher than 0.1 kg per year. There are a total of 54 emission points; 46 of them into rivers and eight into lakes. The color of the circle indicates the release category as defined by the legend, the area of the circle is proportional to the amount of PLGA release. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
Southern Switzerland, Aare north of Berne and again close to Solothurn, Sarine close to Fribourg, Rhine in Basel, and into Lake Geneva. These release points are marked in dark-orange in Fig. 3.

Emissions higher than 0.5 kg/year were calculated at four further locations: two into rivers and two into lakes. These locations are marked in light-orange below. At 42 further locations, emissions higher than 0.1 kg/year were calculated. These locations are shown as small yellow dots. In total 54 emission points higher than 0.1 kg/year were calculated, 46 emission points into rivers and eight into lakes. All emission points higher than 0.1 kg/year are shown in Fig. 3. Size and color of the circle show the release according to the legend.

In a next step, we looked at each of these emission points and at the source of the PLGA which is excreted there. We classified the source either as hospital-affected meaning the PLGA was excreted at a hospital, or as population-affected, meaning that the PLGA was excreted at home after the patient has left the hospital. At 94% (2179 of the 2324) of the emission points, the sole source of emissions comes from population and there is no release from hospitals at this point at all (see Figure A4 in the Supporting Information). At 145 emission points (6% of all emission points), there is at least some release of PLGA from hospitals. Figure A4 in the Supporting Information shows the source of PLGA release for all 2324 emission points. On the x-axis is a thin bar of each of the 2324 emission point with its source indicated in red coming from population in red (excretion at home) or hospital in blue (excretion at a hospital). The y-axis shows the percentage, meaning all emissions are normalized and the amount of PLGA released at each emission point is not shown. If at a certain emission point, no hospital is connected and all PLGA is excreted at home, then the bar is completely red. If at a certain emission point half of all the PLGA emitted is excreted at a hospital and half at home, then half of the bar is red, the other half blue. The emission points are sorted by increasing release from hospitals and not by total emissions.

In a next step, we focused on the release from hospitals. For this, Fig. 4 shows a close up at the emission points with release from hospitals, representing the last 170 emission points from Figure A4. While the first 25 emission points shown in the figure have no release from hospitals at all, the next emission point already has 38% release from hospital. The proportion of release from hospital reaches 80% just 10 emission points later. In total, 106 emission points have a release from hospitals of 95% or more.

When considering only the 54 emission points with releases of more than 0.1 kg per year, the vast majority of the release originates at the hospitals. At these emissions points, more than 85% of the PLGA originates from hospitals, at 42 emission point even more than 95%. The source of PLGA at emission points with releases higher than 0.1 kg/year is shown in the Supporting Information in Figure A5.

3.3. Environmental concentrations

Swiss average wc-PECs are shown in Table 1 as means with upper and lower quantiles (Q25 and Q75) in parentheses. The European values calculated in our previous paper (Hauser and Nowack, 2021) are shown as well for comparison. Sewage sludge is completely incinerated in Switzerland, so no release of PLGA to biosolid-treated soil occurs and therefore no wc-PEC was calculated. The wc-PEC values for all compartments in Switzerland and Europe are of similar magnitude. The highest PLGA concentration was found for sludge which was slightly higher than the average calculated concentrations for sediments. The wc-PECs for surface water are two orders of magnitude lower than those for sediments.

Using the local emissions and the river discharge, we were able to calculate local concentrations of PLGA in river segments with high emissions of PLGA from hospitals (total release more than 0.1 kg per year). No environmental concentrations were calculated for lakes as discussed further below.

The concentration map for rivers shows a completely different picture than the release map seen previously. The highest concentration was calculated south of Basel in Liestal with a concentration of 7900 pg/l. Similar concentrations were calculated in the towns of Alstätten close to the Austrian border with 7500 pg/l and Frauenfeld with 6500 pg/l. The locations are shown in Fig. 5 by a large red circle. These are by far the highest concentrations, the next highest concentration was calculated with 2400 pg/l southwest of St. Gallen.

![Fig. 4. Source of PLGA at the 170 highest emission points (out of 2324) classified as either from hospital or from home (general population). The complete figure with all emission points is shown in the Supporting Information, Figure A4.](image-url)
At 15 locations concentrations higher than the average Swiss wc-PEC for surface water were calculated. The location with the highest local wc-PEC is 13 times higher than the Swiss average. At six locations, even the Q25 exceeds the Swiss average wc-PEC. Fig. 6 shows the local average wc-PEC in ascending order including the Q75 and Q25 for each location.

Comparing Figs. 3 and 5, we can see that the locations with high release do not correspond to locations with high concentration. In Fig. 7, we compare the PLGA release shown in Fig. 3 with the concentration shown in Fig. 5. All releases (>0.1 kg/year) into rivers are taken into account. Three blue dots stand out in the upper left corner of the figure. These are the three locations with high concentration mentioned before. The three river segments with high concentrations have a relatively low release but very low discharge resulting in a high concentration. The release at these three emission points is between 0.2 and 0.4 kg/year. The discharge of the receiving river segment is between 0.7 and 1.9 m$^3$/s. Therefore, the local concentration is mainly influenced by the discharge of the river segment and not by the total release of PLGA.

4. Discussion

We clearly showed that releases of PLGA vary significantly throughout Switzerland. The highest release points were always in close proximity to large hospitals. Comparing Figure A1 in the Supporting...

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Fig. 5. Worst-case predicted environmental concentration of PLGA in 46 river segments with releases >0.1 kg PLGA/year. The color of the circle indicates the concentration category as defined by the legend, the area of the circle is proportional to the PLGA concentration. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 6. Comparison of worst-case predicted environmental concentration of different river segments (blue bar Q25 to Q75, black dot = mean value) compared to average Swiss worst-case predicted concentrations (black line = Swiss mean, gray lines = Q25; Q75). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
Information (showing the location and size of hospitals in Switzerland) with Fig. 3 (showing the location of PLGA emission points), an almost complete overlap of the location and the size of the dot can be found. At locations with a large hospital (large dot) in Figure A1, there was always also a high emission (large dot) in Fig. 3. In Geneva, where the highest emission occurred, there are two hospitals nearby: Les Hôpitaux Universitaires de Genève (HUG) and Clinique Générale-Beaulieu. The HUG is the hospital with the most care days in Switzerland. Therefore, it is obvious that the largest emission will occur there. The same is true in Zurich, where eight different hospitals are located. Other large hospitals occur in Lausanne and Bellinzona and both locations have therefore large emission hotspots. Large hospitals are often located in large cities and are therefore correlated to a high population density, e.g. Geneva and Zurich are the two largest cities in Switzerland. The same spatial variability of population has been used by Kilgallon et al. (2017) to predict higher concentrations of pharmaceuticals in cities. However, large emissions do not always translate to high concentrations as the second part of our study showed. While by far the largest emission occurred around Geneva and Zurich, the local concentrations there were calculated to be low, even below the Swiss average. Historically, large cities were often founded on larger rivers to facilitate transport by ships and this is also true for Geneva and Zurich. The treated wastewater in Geneva is released in the river Rhône, one of the largest rivers in Switzerland. In Zurich, the treated wastewater is released in the river Limmat, also a fairly large river. Therefore, the emissions are highly diluted and the resulting concentrations low. Al Aukidy et al. (2014) modelled 32 different pharmaceuticals looking at three different hospitals and taking into consideration characteristics such as the number of beds and water consumption of the hospital, number of inhabitants and water demand of the catchment area, treatment processes used for the hospital effluent, and the dilution and hydrodynamic features of the receiving water body. While we concluded that river discharge is the main influence of the concentration, the authors concluded that the contribution of a hospital effluent to the environmental risk is correlated to its bed density. On the other hand, in this study we observed high concentrations PLGA in the towns of Albstätten close to the Austrian border, Liestal close to Basel or Frauenfeld in Eastern Switzerland, where the rivers receiving the treated wastewater have a very low discharge. Therefore even small emissions can result in high local concentrations, if the discharge of the river is small.

A large release into lakes were calculated for Lake Geneva with 1.9 kg/year. However, Lake Geneva is a large lake with an area of 580 km² and depending on the currents, estuaries and release load from different WWTPs, the release can vary in different areas of the lake. To rectify this, a Lagrangian model similar to the one used by Fonseca et al. (2020) could be applied. Fonseca et al. (2020) calculated the exposure potential of different pharmaceuticals in the Tagus estuary in Portugal to identify areas of ecological relevance prone to environmental degradation due to increased exposure of emerging contaminants. A similar approach would highlight hotspots of NBM release in the Swiss lakes and could be particularly interesting for larger lakes with several inflows such as Lake Geneva. Around Lausanne, there are several hospitals and WWTPs, which release their wastewater directly into the lake. The model developed here only shows the releases of NBMs to the environment but does not consider possible transport and fate of the NBMs once they are in the environment. The reported wc-PECs are valid for a situation very close to the emission point when no fate process such as biodegradation or sedimentation have affected the suspended concentration of PLGA. Data on fate processes of NBMs such as degradation in river water, their ability to aggregate to solid matrices and the occurrence of physical-chemical transformation are not yet available but are needed in order to parameterize a fate model for nanoparticles such as Simple-Box4Nano (Meesters et al., 2014). Thus, in a further study, these processes could be first studied and quantified to allow a coupling of the release model with a fate model to calculate predicted environmental concentrations of the NBMs for several environmental compartments as has been done by Lindim et al. (2017) for pharmaceuticals in Swedish waters. However, these fate processes would further diminish the concentrations of NBM that are predicted to be in the pg/l range in our worst-case assessment.

We refrained from calculating environmental concentrations in lakes, even though there were large emissions into some lakes. Lakes have a very large volume and a long residence time of water of up to several years (Ambrosetti et al., 2003). During this time, fate processes such as sedimentation, agglomeration or degradation would occur. As our model does not include these processes, the calculated concentrations would be wildly unreliable. In addition, PLGA has been shown to metabolize in the body within four weeks (Gentile et al., 2014). Assuming a similar degradation rate in water, the PLGA would be transformed long before the water leaves the lake. To obtain PEC values in lakes, using an environmental fate model is therefore indispensable but was beyond the scope of this study which was targeted on quantifying the release.

Ideally, the calculated wc-PEC values would be compared to PNEC values for a complete environmental risk assessment. However, no ecotoxicological data for PLGA is available to date. Freshwater PNEC values were reported for the polymeric nanomaterials chitosan and polycrylonitrile (PAN) by Hauser et al. (2019). Even chitosan, the most toxic of the evaluated polymeric nanomaterials has a PNEC value in

![Fig. 7. Comparing the release of PLGA into rivers with the resulting concentration of PLGA in this river segment.](image-url)
freshwater of 5.0 (Q25: 4.0; Q75: 6.0) μg/l, which is more than 6000 times higher than our wc-PEC for PLGA of 600 (250; 690) μg/l. The value for PAN, another organic polymer, is orders of magnitude higher. Therefore, we do not expect that PLGA poses any risk to freshwaters, not even at the release points with the highest local concentration.

Often the modelled environmental concentrations are compared to measured data to validate the model (Kilgallon et al., 2017; Lindim et al., 2017). However, in this case, it is not possible yet. The use of PLGA to aid the delivery of cancer drugs is still in the development phase and not yet on the market. Therefore, no release of PLGA has occurred to the environment yet. As mentioned before, our model shows an explorative full market-penetration scenario estimating the maximum possible future flows of PLGA. Once these applications of PLGA become commonly available, it will be interesting to take measurements in order to compare and validate the current model.

Even though our model has calculated local emissions and concentrations of PLGA emissions, we still only considered average releases and concentrations throughout one year. The discharge of rivers varies considerably throughout the year. We used an average discharge calculated over several years. This gives a good approximation but does not consider the yearly fluctuation. Especially at locations with already high concentrations, these fluctuations could increase the concentration even more. In a further step, these seasonal variations could be added to the current model.

The model assumed that 95% of the PLGA would be excreted at the hospital and the remaining 5% at home. This 5% was distributed to the different WWTPs based on the whole population. However, using the whole populations might be an oversimplification. Older age groups are more likely to develop cancer and therefore be treated with cancer drugs and PLGA. Therefore, a future addition to the model could use spatial data on older age groups and mainly include them for the distribution of the 5% excreted at home.

In summary, the current study gives a good overview of possible hotspots of future PLGA releases. We have shown that not the total amount of PLGA release is the main factor contributing to high concentrations but the river discharge. Often high concentrations were calculated in towns with smaller hospitals but also smaller rivers with low discharge. In large cities, which are located at large rivers, the PLGA is highly diluted leading to low concentrations. Therefore, population density cannot identify the hotspots of PLGA releases.

Once these PLGA applications become available, the locations highlighted in the study would need to be monitored carefully to detect possible high PLGA concentrations early. Besides PLGA, there are a wide range of other NBMs or pharmaceuticals, which are predominantly found in wastewater. Therefore, a future addition to this model would need to be monitored carefully to detect possible high concentrations of these pharmaceuticals as well. Even though their environmental concentration will differ from PLGA, the location of high concentration will be the same.

5. Conclusions

In this study, we calculated possible prospective local releases and local concentrations for PLGA from medical usage in Switzerland using GIS data on hospitals, WWTPs, river networks and lakes. While we predicted high releases to occur around big cities, the expected concentrations there were low. In the past, large cities were often found on large rivers with high discharge. Therefore, even though the release at these cities is large, dilution leads to low concentrations. On the other hand, we predict high concentrations to occur at medium-sized hospitals where the treated wastewater is released into a small stream. Even though our study was conducted for PLGA, the same hotspots of high concentrations are possible for other materials used in hospital settings.

Author contributions

MH collected, prepared, and evaluated the input data. MH also ran the model, created the figures and tables for the manuscript, and wrote the manuscript. BN supervised the study, gave inputs on the data and the model, and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envrpol.2021.117399.

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