A survey of industrial N-nitrosamine discharges in Switzerland

Florian Breider,*, Caroline Gachet Aquillon, Urs von Gunten

a Ecole Polytechnique Fédérale de Lausanne (EPFL), ENAC, IIE, CH-1015 Lausanne, Switzerland
b Eawag, Swiss Federal Institute of Aquatic Science and Technology, CH-8600 Dubendorf, Switzerland

HIGHLIGHTS

• 4 N-nitrosamines out 8 were detected in the effluents of eight industrial sites.
• High NDMA concentrations are released by industries (0.2–975 μg/L).
• Industrial compared to municipal discharges are more important for N-nitrosamines.

ABSTRACT

N-nitrosamines are formed during different industrial processes and are of significant concern due to their carcinogenic and mutagenic properties. This study reports concentrations of N-nitrosamines in eight different industrial wastewater treatment plants in Switzerland and the variability of their abundance. Only four N-nitrosamines species, N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosodibutylamine (NDPA) and N-nitrosomorpholine (NMOR) were above the limit of quantification in this campaign. Remarkably high concentrations (i.e. up to 975 μg NDMA/L, 90.7 μg NDEA/L, 1.6 μg NDPA/L and 710 μg NMOR/L) of these N-nitrosamines were detected at seven of eight sites. These concentrations are two to five orders of magnitude higher than those typically detected in municipal wastewater effluents. These results suggest that industrial effluents may be a major source of N-nitrosamines. Although very high concentrations of N-nitrosamine have been detected in industrial discharges, various processes in surface water can partially mitigate their concentrations (e.g. photolysis, biodegradation and volatilization) and hence the risk to human health and aquatic ecosystems. Nevertheless, there is little information on long-term effects on aquatic organisms and therefore the discharge of N-nitrosamines to the environment should be avoided until the impact on ecosystems is assessed. During winter a less efficient mitigation of N-nitrosamines can be expected (lower biological activity, less sunlight) and therefore, emphasis should be put on this season in future risk assessment studies.

* Corresponding author.
** Corresponding author at: Ecole Polytechnique Fédérale de Lausanne (EPFL), ENAC, IIE, CH-1015 Lausanne, Switzerland.
E-mail addresses: florian.breider@epfl.ch (F. Breider), urs.vongunten@epfl.ch (U. von Gunten).
1. Introduction

The presence of N-nitrosamines in water resources has received considerable attention because of their mutagenic and carcinogenic potential. So far nine alkyl N-nitrosamines, i.e., N-nitrosodimethylamine (NDMA), N-nitrosomethylethylamine (NMEA), N-nitrosodimethylurea (NNDU), N-nitrosodimethylamine (NDMA), N-nitrosopyrrolidine (NPIP), and N-nitrosomorpholine (NMOR) were studied. These N-nitrosamines have been identified as disinfection by-products during chlorination and ozonation of wastewater and in chloraminated drinking water [1,14,22,5]. In the United States, the formation of NDMA is mainly attributed to the use of monochloramine for the disinfection of drinking water or wastewater [17,31]. N-nitrosamines are generally unintentionally produced substances. Apart from the occurrence as a disinfection by-product, N-nitrosamines can be formed in a range of industrial processes in which amines get into contact with nitrogen oxides, nitrous acid, or nitrite [15]. For instance, N-nitrosamine formation has been associated with rubber manufacturing and processing, leather tanning, metal casting, metalworking using cutting fluids, electronic industry and food processing [25,28,4,9]. For instance in samples from discharges of a printed circuit board manufacturer using diethiocarbamate-based compounds up to 4500 ng/L NDMA were reported [6,23]. Furthermore, recently, several studies have shown that N-nitrosamines are unintentionally formed during the production process of certain pharmaceuticals [26]. Pallez et al. [18] found NMOR concentrations of up to 3000 ng/L in wastewater treatment plants (WWTPs) in Switzerland [15]. Concentrations of NDEA, NPIP and NDBA were generally determined during the production process of certain pharmaceuticals [26,27]. Krauss et al. [15] have shown that NDMA and NMOR are the predominant compounds among eight N-nitrosamines selected by US Environmental Protection Agency (USEPA) in 21 full-scale municipal wastewater treatment plants (WWTPs) in Switzerland [15]. Concentrations of NDEA, NPIP and NDBA were generally < 5 ng/L and NMEA and NPYR were not detected in any secondary effluent except one wastewater treatment plant. The NMOR concentrations ranged from 3 to 26 ng/L. The median concentrations of NDMA in primary and secondary effluents of municipal WWTPs ranged between 5 and 20 ng/L, with peak concentrations of < 1 µg/L. Such concentration peaks are suspected to be caused by industrial discharges, resulting in highly variable N-nitrosamine concentrations in municipal wastewater [3,15]. Similar NDMA concentration peaks likely associated with industrial discharges from printed circuit board manufacturing facilities were also observed in the USA in influent and primary effluent samples from municipal WWTPs [23]. Recently, it has been demonstrated that WWTP effluents are a major source of synthetic organic contaminants to the aquatic environment [2]. However, it is currently unclear whether N-nitrosamine emissions from chemical and pharmaceutical manufacturing are isolated events or widespread. Moreover, the origin of N-nitrosamines in industrial wastewater is poorly understood and the occurrence and variability of N-nitrosamines concentrations in industrial discharges have never been assessed in Switzerland. Therefore, a better assessment of the contribution of industrial effluents to the load of N-nitrosamines in surface waters and municipal wastewaters is necessary to develop mitigation strategies.

The aim of this study was to assess the occurrence and variability of N-nitrosamines in discharges from chemical and pharmaceutical manufacturing and industries treating chemical wastes. Industrial wastewaters were sampled on a national scale to evaluate their relevance as N-nitrosamine sources affecting water quality. Specifically, the following issues were addressed: (i) Investigation of the occurrence of eight N-nitrosamines in industrial WWTPs in Switzerland, (ii) assessment of the temporal variability of N-nitrosamines concentrations in industrial effluents and (iii) assessment of the contribution of industries as a source of N-nitrosamines to the aquatic environment. To achieve these goals, water samples were collected at different times at eight industrial sites from different sectors and were analysed by GC-MS/MS for N-nitrosamines.

2. Materials and methods

2.1. Chemicals and reagents

EPA 8270/Appendix IX Nitrosamines Mix, a certified reference material, 2000 µg/mL each component in MeOH, Supelco (prod. 50213) was purchased from Sigma-Aldrich. N-nitrosodimethylamine-d6 (prod. AX15605010AC) (100 ng/µL in acetone), N-nitroso-N-dipropylamine-d14 (prod. XA15605010AC, 100 ng/µL) in acetone were purchased by Ehrenstorfer. N-nitrosomorpholine-d8 (prod. DLM-8254–1.2; 1 mg/mL in CD2Cl2), N-nitrosodimethylamine-d10 (prod. DLM-7982–S; 1 mg/mL in CD2Cl2), N-nitrosopyrrolidine-d8 (prod. N’ DLM8252–1.2) (1 mg/mL in CD2Cl2), were obtained at Cambridge Isotope Laboratories. N-nitrosodi-n-butylamine-d18 (prod. D67711) 50 mg, N-nitrosopiperidine-d10 (prod. N’ D-4139) 50 mg were purchased by CDN Isotopes. Dichloromethane RS Isocratic grade for HPLC (prod. 412622000) and methanol RS Gold for HPLC (prod. 412372000) were obtained from Carlo-Erba. Sodium sulfate anhydrous (prod. 239313) was purchased from Sigma-Aldrich. Argon 99.9999% (Alphagaz 2), Helium 99.999% (Alphagaz 1) and Nitrogen 99.999% (Alphagaz 1) were purchased from Carbagas.

The N-nitrosamine standard solutions were prepared as follow: EPA Mix Stock A solution 10 µg/mL was prepared by dilution of 50 µL of EPA Mix 2000 µg/mL in 10 mL dichloromethane. NDBA-d18 solution 2000 µg/L was prepared by dissolution of 10 mg of pure compound in 5 mL dichloromethane. Internal standards stock A solution 2.5 µg/mL was prepared by dilution of 250 µL of NMDA-d6 100 µg/mL plus 12.5 µL of NDBA-d18 2000 µg/L in 10 mL dichloromethane. Internal standard stock B solution 0.25 µg/mL was prepared by dilution of 1000 µL of internal standard stock A in 10 mL dichloromethane. NPIP-d10 solution 2000 µg/L was prepared by dissolution of 12.5 µg of pure compound in 5 mL dichloromethane. Surrogate stock A solution 2.5 µg/mL was prepared by dilution of 25 µL of NDEA-d10 1000 µg/mL, NPIP-d8 1000 µg/mL, NMDR-d8 1000 µg/mL, and NDBA-d18 12.5 µL of NMDA-d6 2000 µg/L and 250 µL of NDBA-d14 100 µg/mL in 10 mL methanol. Calibrating standard solutions were prepared by further dilution of the EPA Mix Stock A solution 10 mg/mL and internal standard stock A solution 2.5 mg/mL, to achieve concentrations of 5, 10, 25, 50, 100, 250 µg/L of each nitrosamine and a level of 50 mg/L of internal standard. Control surrogate standard solutions were prepared by further dilutions of surrogate stock A solution 2.5 mg/mL and internal standard stock A solution 2.5 mg/mL, to achieve concentrations of 25, 50, 75, µg/L of each surrogate and a level of 50 mg/L of internal standard. All stock solutions were stored in the dark at 4 °C.

2.2. Sampling procedure and sites description

Composite samples of 500–1000 mL from eight industrial sites located in Switzerland were collected over 24, 72, 96 or 120-h between November 2017 and June 2021 (Table 1). All industrial sites selected for this study are chemical or pharmaceutical factories, companies treating hazardous wastes or a municipal wastewater treatment plant with a large industrial contribution. Site A is a municipal WWTP with large contribution of various industrial wastewaters. Site B is a company treating various chemical and hazardous industrial wastewaters and cleaning tank cars used for the transportation of chemical substances. Site C consists of a WWTP treating chemical wastewater. Site D is a WWTP which treats wastewater from industry and municipalities. The company of the site E is treating organic and inorganic chemical wastes from various industries. Finally, sites F, G and H correspond to industrial wastewater of chemical companies synthesizing various high value organic compounds. To minimize variability associated with flows of industrial wastewater, 1-day (sites E and F), 3-days (site C), 4-days (sites G, H), 5-days (site B and D) and 7-days (site A) flow proportional...
composite samples were collected. The sampling periods were different between the sites to match with the general operation patterns of the different industrial facilities. To minimize variations in wastewater composition from industrial sources, most samples were collected on week days, when industrial activities were at their highest levels. All of the composite samples were collected in brown glass sample containers. Immediately after collection, composite samples were filtered with glass microfiber filters (2.7 µm) and nylon membrane filters (0.45 µm) and stored at 4 °C for a maximum of a week before analysis.

### 2.3. Sample preparation and analyses

Most samples were pre-concentrated by solid phase extraction (SPE). However, samples containing fine particles (< 0.45 µm) were pre-concentrated by liquid-liquid extraction to avoid clogging of SPE cartridges (Table 1). The SPE extraction was performed as follows: Supelclean Coconut Charcoal cartridges (2 g/6 mL; Supelco n° 57144-U) were installed on a parallel elution and evaporation instrument (Synore, Büchi) and activated with 2 × 3 mL of dichloromethane, 2 × 3 mL of methanol and then with 4 × 3 mL of ultrapure water. Then, the cartridges were loaded with 1 L of sample using PTFE tubes and with a slight vacuum (~700–800 mbar) to obtain a flow of about 1 drop/sec and rinsed with 5 mL of ultrapure water. The cartridges were dried under a nitrogen stream at 1 bar for 2 h. The SPE cartridges were eluted with 4 × 3 mL of dichloromethane and the extracts were collected in 15 mL brown tared flasks. To eliminate residual water, extracts were filtered through a SPE glass pack with 6 g of anhydrous sodium sulphate (the drying column was pre-wetted with 1.5 mL of dichloromethane). The extracts were then dried under a nitrogen stream at 0.2 bar to partially evaporate the solvent until a weight of 1 g. Finally, 200 µL of concentrated sample was transferred to a 1.5 mL brown vial with a 350 µL insert and 50 µL of an isotope-labelled N-nitrosamine standard stock solution (250 µg/L) was added to the samples.

The samples pre-concentrated by liquid-liquid extraction were prepared as follows: 50 mL of sample was extracted with 3 × 20 mL of dichloromethane and the extracts were collected in Erlenmeyer flasks and dried by adding ~5 g of anhydrous sodium sulphate. The extracts were filtered with a cellulose filter (Whatman 597, diam. 125 mm) and rinsed with 3 × 3 mL of dichloromethane. The solvent was partly evaporated at 800–850 mbar and 40 °C. The solvent residual was transferred in a 15 mL tared vial and evaporated to 1 mL under a slight nitrogen stream. Finally, 200 µL of the concentrated sample was transferred to a 1.5 mL brown vial with a 350 µL insert and 50 µL of an isotope-labelled N-nitrosamines standard stock solution (250 µg/L) was added to the samples.

The pre-concentrated samples were analysed by large volume injection gas chromatography and electron ionization tandem mass spectrometry (LVI-GC-MS/MS). The method used was developed to analyse nine reference N-nitrosamines and is based on method 521 previously developed by the USEPA [27] (For more information see supporting information). However, NDPhA was not quantified in this study since other compounds interfered with this N-nitrosamine. The limits of detection and quantification of the LVI-GC-MS/MS method developed for this study were determined based on twelve injections of 20 µL of a standard solution of the USEPA 8270 N-nitrosamines mix at 5 ppb (0.1 ng on column; Table 2). With the GC-MS/MS method developed on a triple quadrupole system (TSQ Quantum XLS ultra® system, Thermo Scientific) all N-nitrosamines under investigation could be safely detected and precisely quantified at the required low levels.

### 2.4. Method performance

Method performance, analyte detection and quantification limits were assessed by performing matrix spike experiments. A complete list of average recoveries in ultrapure water and wastewater effluent for both solid-phase and liquid-liquid extractions, the minimum and maximum limits of detection (LOD) and quantification (LOQ) for each screened N-nitrosamine is provided in Table 2. The recovery of the screened N-nitrosamines range between 59% and 88% in ultrapure water and between 20% and 95% in municipal wastewater effluent (pH 8.1, DOC: 8.7 mg /L; NH4+: 19.16 mg N/L; NO2: 0.006 mg N/L, NO3: 0.02 mg N/L, alkalinity: 5.21 mM). The low recovery efficiency obtained for NDPA in wastewater is likely due the high background signal from interfering compounds. There is no significant difference in the recovery of NDMA, NMEA, NDEA, NDBA and NPYR between spiked ultrapure water and wastewater (p-value <5). The average recoveries of these N-nitrosamines were ≥ 59% in ultrapure water and ≥ 45% in wastewater. These values are consistent with values previously reported in the literature for N-nitrosamines in complex environmental matrices [10, 15]. An average recovery of only 20% was measured for NDPA in wastewater whereas its recovery in ultrapure water was 62%. LOD and LOQ for the various N-nitrosamines ranged from 0.05 and 2.83 µg/L and from 0.55 and 9.43 µg/L, respectively (Table 2). Process control samples and blanks showed no laboratory contamination.

### 3. Results and discussion

#### 3.1. Occurrence of N-nitrosamines in industrial wastewaters

The analysis of the water samples collected at the selected eight sites have shown that only four N-nitrosamines (i.e., NDMA, NDEA, NDBA and NMOR) from the eight targeted N-nitrosamines were > LOQ (Fig. 1). However, this result does not mean that other potentially toxic N-nitrosamines with structures different from those targeted in this study are not present in industrial effluents. It has been demonstrated that the N-nitrosamines analysed with the USEPA 521 method represent sometimes only a small fraction of the total N-nitrosamine concentration [30,31]. The median NDMA, NDEA, NDBA and NMOR concentrations were 36.3, 1.7, 0.1 and 0.2 µg/L respectively. NDMA and NMOR are the most abundant N-nitrosamines measured in industrial effluents with maximum concentrations of < 975 µg/L for NDMA and < 710 µg/L for NMOR. In contrast the maximum measured concentrations of NDEA and

### Table 1

Industrial wastewater effluents samples collected in seven geographical regions across Switzerland.

<table>
<thead>
<tr>
<th>Site</th>
<th>Category of industry</th>
<th>Location</th>
<th>Sampling period</th>
<th>Sampling interval</th>
<th>Pre-concentration method</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Municipal WWTP with high industrial contribution</td>
<td>GL</td>
<td>14.01.19–03.02.20</td>
<td>24 h</td>
<td>Solid phase extraction</td>
</tr>
<tr>
<td>B</td>
<td>Industrial waste treatment</td>
<td>AG</td>
<td>08.04.19–26.04.19</td>
<td>120 h</td>
<td>Liquid-liquid extraction</td>
</tr>
<tr>
<td>C</td>
<td>Chemical / pharmaceutical</td>
<td>BS</td>
<td>06.05.19–22.05.19</td>
<td>72 h</td>
<td>Solid phase extraction</td>
</tr>
<tr>
<td>D</td>
<td>Chemical / pharmaceutical</td>
<td>BL</td>
<td>12.08.19–30.08.19</td>
<td>120 h</td>
<td>Liquid-liquid extraction</td>
</tr>
<tr>
<td>E</td>
<td>Industrial waste treatment</td>
<td>NE</td>
<td>02.11.20–27.11.20</td>
<td>24 h</td>
<td>Liquid-liquid extraction</td>
</tr>
<tr>
<td>F</td>
<td>Chemical</td>
<td>GE</td>
<td>15.03.21–26.03.21</td>
<td>24 h</td>
<td>Liquid-liquid extraction</td>
</tr>
<tr>
<td>G</td>
<td>Chemical / pharmaceutical</td>
<td>VS</td>
<td>13.11.17–19.01.18</td>
<td>96 h</td>
<td>Solid phase extraction</td>
</tr>
<tr>
<td>H</td>
<td>Chemical</td>
<td>VS</td>
<td>13.11.17–19.01.18</td>
<td>96 h</td>
<td>Solid phase extraction</td>
</tr>
</tbody>
</table>

* The location corresponds to the cantons where the company is located: Glarus (GL), Aargau (AG), Baselstadt (BS), Basellandschaft (BL), Neuchâtel (NE), Genève (GE), Valais (VS).

1. Interval of time between sampling (flow proportional sampling)
The concentrations of the detected N-nitrosamines were highly variable at each site and between the different sites (Fig. 1). This variability reflects the important temporal variation of the N-nitrosamines concentrations in the industrial effluents and the type of industrial activities at the sampling sites. The mean concentrations of NDMA were ≥1 µg/L for all sites except site F where it was <LOQ (Table 3). Inversely, the mean concentrations of NDBA were ≤1 µg/L at all sites except site E where the mean concentration was slightly above this threshold (1.6 µg/L).

At sites A, C and D the mean concentrations of NDMA were ≥1 µg/L, whereas for NDEA, NDBA and NMOR they were either <LOD or between 0.01 and 0.3 µg/L (Table 3). Sites B and E which treat organic and inorganic chemical wastes from various industries show similar N-nitrosamines concentration patterns, with NDMA and NMOR concentrations one to two orders of magnitude higher than NDEA and NDBA concentrations (Table 3). However, at site E the mean concentrations of NDMA, NDEA, NDBA and NMOR were all ≥1 µg/L, whereas at site B, the mean NDBA concentrations were <1 µg/L. Both sites are characterized by very high mean NMOR concentrations (site B 10.5 µg/L and site E 325.5 µg/L) compared to the other sites where the mean NMOR concentrations are all ≤0.2 µg/L. These NMOR concentrations were well above concentrations previously measured in municipal wastewater effluents (1390 ng/L) [22]. Morpholine, the amine precursor of NMOR, is used for many industrial applications such as rubber additives, corrosion inhibitors, solvents, optical brighteners, antioxidants and in the manufacturing of a range of drugs and herbicides. Consequently, these compounds can occur in various industrials effluents and therefore it is not surprising to detect high concentrations in the wastewater from chemical and pharmaceutical industries and companies handling industrial chemical waste. Pallez et al. [18] also measured high NMOR concentrations in a river downstream a pharmaceutical site where...
Fig. 2. Variation of the NDMA (red bars), NDEA (yellow bars), NDBA (green bars), NMOR (blue bars) concentrations at the eight sites for the selected sampling periods. A-H: sites according to Table 1.
several thousand tons of morpholine are used for manufacturing [18]. At site F all targeted N-nitrosamines were < 1 μg/L and this is also the only site where NDMA was not detected. In contrast at sites G and H, NDMA and NDEA mean concentrations were ≥ 1 μg/L, whereas NDBA and NMOR mean concentrations were < 1 μg/L. Although sites C, D, F, G and H are all chemical or pharmaceutical companies, the concentration range of N-nitrosamines vary over several orders of magnitude. These differences in N-nitrosamine concentrations are likely related to differences in the processes and chemicals used by these companies.

Fig. 2 shows measured N-nitrosamines concentrations for the sites A-H at various sampling times. The concentrations of NDMA, NDEA, NDBA and NMOR measured in this study are rather stable for different sampling time points. This is different at the sites D and G where the NDMA concentration decreases by about four orders of magnitude between the beginning and the end of the sampling campaign and at site E where NDEA concentrations where below the LOD on three sampling dates (24–26.11.2020). These results suggest that at most of the sampling sites the source of N-nitrosamines was rather constant during the sampling period, whereas the strong decline of NDMA and NDEA concentrations at sites D, E and G might be due to changes in the industrial processes during the sampling period (e.g., modification of products with different chemicals, temperature, pH, etc.). Because of the variation of N-nitrosamine levels and types detected at different sampling sites, it can be hypothesized that N-nitrosamine formation is unintentional and likely results from many different chemical reactions and industrial processes for instance where nitrite and amines are present simultaneously (possibly under acidic conditions) or during oxidation processes [11,13,31]. Episodic spikes in NDMA and NMOR concentrations in Swiss municipal wastewaters were detected in previous studies and it was hypothesized that this was related to industrial discharges [3,15]. The elevated concentrations measured in the present study in industrial wastewaters supports this hypothesis and suggests that industrial discharges are a major source of N-nitrosamines in aquatic systems.

3.2. Toxicological risk associated with N-nitrosamines in industrial discharges

N-nitrosamines in industrial discharges may not pose an immediate cancer risk to humans because there is no direct route of oral or respiratory exposure. However, industrial effluents are frequently discharged in municipal wastewater systems or in surface waters. This has the potential to create an indirect route of oral exposure in case of direct and indirect water reuse. Furthermore, rivers and lakes are commonly used for recreational water uses (e.g. swimming and other water sports), which may contribute to inadvertent human exposure to N-nitrosamines from either accidental or deliberate water ingestion. To further assess the carcinogenic risk associated to N-nitrosamine industrial discharges, the dilution factors required to reach a risk level of 10⁻⁵ which corresponds to the N-nitrosamine-specific concentrations providing cancer risks of one case in a population of 100,000 individuals determined by the USEPA in the lowest and highest mean concentrations measured in this study (Table 4). This cancer risk level was chosen since a cancer risk level of 10⁻⁵ could be seen as indicative of tolerable risks levels in the general population. This risk assessment considers a scenario of a lifetime consumption of 2 L of water per day and doesn’t apply to recreational water uses such as swimming. The results show that a dilution factor ranging from about 200 and 36,400-fold would be required to reach NDMA concentrations below the cancer risks threshold set in this study. A corresponding dilution factor is ranging from about 25–26,900-fold for NDEA whereas it ranges only between about 0.15 and 27-fold for NDBA since this latter compound is slightly less toxic than NDMA and NDEA and less abundant in industrial discharges. The dilution factor required for NMOR was not calculated since the concentration providing cancer risks of one case in a population of 100,000 individuals was not determined by the USEPA. However, if we consider that the drinking water concentration of NMOR at specific risk level of 10⁻⁵ is in the same range as for the three other N-nitrosamines, a maximum dilution factor ranging between ~5’000 and 15’000-fold would be required in some specific cases such as the sampling site E where NMOR concentration reached up to 300 μg/L. In 2008, the World Health Organisation established a guideline value of 100 ng/L for NDMA in drinking water [16]. To comply with this guideline a dilution factor of ~15–25’000-fold would be required.

Industrial wastewater discharge rates vary depending on the type of industrial activity, but generally range from ~5 to > 350 m³/day, while discharge rates from municipal wastewater treatment plants generally range from ~250 to > 50,000 m³/day. Therefore, in the best-case scenario, it can be assumed that industrial discharges can be diluted approximately 10’000 times by municipal wastewater. After treatment, the wastewaters are discharged into surface waters such as lakes and rivers. In Switzerland, medium and large rivers have flow rates several orders of magnitude higher (e.g. ~1 and 500 m³/sec) than the discharge rates of wastewater treatment plants. Therefore, it seems reasonable to assume that the dilution of industrial effluents with municipal wastewater and then into surface waters result in N-nitrosamine concentrations lower than the risk level 10⁻⁵. Moreover, it has been demonstrated that N-nitrosamines are well biodegradable in biological post-filtration processes such as sand and activated carbon filtration which are often used in WWTP [20,21,3]. In laboratory incubation experiments NDMA was shown to be biodegraded in unsaturated and saturated soil samples under both aerobic and anaerobic conditions [32]. Moreover a significant biodegradation of NDMA occurred in some aquifers [32]. Photolysis by sunlight induces the cleavage of the N-N bond of the N-nitroso group leading to the formation of NO radicals and a secondary amine. It was demonstrated that photolysis is the degradation mechanism that contributes most to the abatement of NDMA compared to volatilization and biodegradation in a drinking water treatment plant [20]. Moreover, it was shown that including UV treatment in industrial water treatment could significantly reduce NMOR discharges from a pharmaceutical site using large quantities of morpholine in its manufacturing process [18]. However, some industrial discharges are almost opaque to UV-C radiation. Hence UV treatment can realistically not be carried out in all cases or only with a significant pre-treatment for turbidity removal. Sunlight-induced photo-degradation processes are quite efficient and likely the main processes for the abatement of N-nitrosamines in surface water, often also in combination with volatilization [19,24]. However, the effectiveness of all natural degradation processes varies with the season. Indeed, in winter the biodegradation processes are slower due to lower temperature, river flows decrease which reduce the dilution of industrial discharges with surface water and the lower sunlight intensity and shorter exposure reduces the photodegradation of N-nitrosamines.

It has been demonstrated that NDBA, NPYR and NDPHA can be

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Drinking water concentrations at risk level of 1 in 100’000 and dilution factors required to reach this specific risk level.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>Measured mean conc.</td>
</tr>
<tr>
<td></td>
<td>(μg/L)</td>
</tr>
<tr>
<td>N-nitrosodimethylamine (NDMA)</td>
<td>1.4</td>
</tr>
<tr>
<td>N-nitrosodiethylamine (NDEA)</td>
<td>0.05</td>
</tr>
<tr>
<td>N-nitrosodibutylamine (NDBA)</td>
<td>0.009</td>
</tr>
<tr>
<td>N-nitrosomorpholine (NMOR)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

a) DWC-10⁻⁵: calculated drinking water concentration at a specific risk level of 1 in 100’000 cases of cancer.
b) DF-10⁻⁵: dilution factor required to reach a risk level of 1 in 100’000 cases of cancer.
adsorbed on sediments because of their relatively high partitioning coefficients [10]. NDMA, NDEA and NMOR detected in industrial discharges are not expected to accumulate in sludge or sediments since their octanol-water partitioning coefficients are low (logKow values: NDMA: −0.57; NDEA: 0.48; NMOR: −0.44).

The eco-toxicological consequences of the discharge of high concentrations such as those measured in this study deserves a brief discussion. Although not all N-nitrosamines have been tested for their ecotoxicity and for adverse mixture effects on aquatic organisms, some LC50 values are available, a 96-h LC50 of 940 mg NDMA/L and 775 mg NDEA/L for fathead minnow (*Pimephales promelas*), a 96-h LC50 of 1365 mg NDMA/L and 1490 mg NDEA/L for flatworms (*Dugesia dorotocephala*) and 96-h LC50 values of 330 mg NDMA/L to 500 mg NDEA/L for *Gammarus limnaeus* [7,8]. These values span over a wide range and are all orders of magnitude higher than the concentrations reported in this study. Even if N-nitrosamine concentrations measured in industrial discharges do not appear to pose a threat in terms of acute toxicity, chronic toxicity problems may occur. For instance, frogs (*Rana temporaria*) exposed to 5 mg/L NDMA in water for 63 days and 203 days developed hepatocellular carcinomas as well as adenomas and tumours of the haematopoietic system. More than 40% of the frogs exposed for 203 days developed tumours [12]. The concentration used in these experiments are orders of magnitude higher than the concentrations measured in the present study. However, it cannot be excluded that a long-term exposure to lower concentrations could have deleterious effects on aquatic organisms. So far only a very limited number of EC50 values are available in the scientific literature. Moreover, not all N-nitrosamines analysed in this study have been tested for their toxicity and for adverse mixture effects in aquatic ecosystems. Therefore, more long-term in-vitro and in-vivo ecotoxicological assays should be conducted to better assess the ecotoxicological impact of a chronic exposure of aquatic organisms to N-nitrosamines.

4. Study limitations, data gaps, and outlook

This study provides novel data on the release of N-nitrosamines from different industrial sites in Switzerland but has a number of limitations. The determination of the processes causing the formation of the detected N-nitrosamines is hampered by the lack of information on the industrial processes used at the different sampling sites. For instance, industrial effluents are neutralised before being discharged into municipal wastewater or directly into the environment. Therefore, there is no information on the pH under which the detected N-nitrosamines were formed. Overall, the complex composition of the industrial discharges makes it practically impossible to identify the chemical mechanisms responsible for the formation of N-nitrosamines. The N-nitrosamines detected are probably the result of several chemical reactions including nitrosation of secondary amines in presence of nitrite under acidic conditions. Chloramination as a source of N-nitrosamines is unlikely since this process is not used to treat wastewater in Switzerland. Therefore, N-nitrosamine formation pathways need to be better understood in industrial processes to develop mitigation strategies. Moreover, an assessment of N-nitrosamine precursors in industrial discharges would be needed in water reuse scenarios.

The number of samples analysed is relatively limited, making the representativeness of this study across Switzerland vulnerable to potential bias. The analysis of more samples from various industries over a wider time period would allow a more accurate assessment of N-nitrosamine discharges and to determine which industrial sectors are the biggest emitters. Some industries maintain their production processes continuously for several months or even years, while others adapt them daily or weekly according to customer demand. This can therefore potentially have consequences in terms of the variability of N-nitrosamine releases. This information would help to determine the measures to be taken to reduce these emissions. Even though there is some information on the fate of N-nitrosamines in the aquatic environment (photo-, biodegradation, adsorption), more information would be needed to make an overall assessment of this compound class. Furthermore, the potential toxicological impacts of the N-nitrosamines discussed in this paper for human health and aquatic ecosystems are estimated based on available data and constitute another important gap in the understanding of potential consequences of N-nitrosamine discharges into the environment.

5. Conclusion

This study provides a general overview of the occurrence of N-nitrosamines in industrial discharges in Switzerland. The following conclusions can be drawn:

The results of this study show that industrial wastewater effluents can contain very high concentrations of N-nitrosamines. The concentrations measured are several orders of magnitude higher than those typically measured in municipal wastewater effluents. These results corroborate the hypothesis that industrial effluents may be responsible for the observed N-nitrosamine concentration peaks measured in some municipal wastewaters in Switzerland. The discharge rates are highly variable and were not available at the time of sampling. However, this study shows that orders of magnitude are sufficient at this stage to assess the impacts of this class of compounds. Nevertheless, a more extensive monitoring of N-nitrosamines emitted by industry would be necessary to assess the impact on ecosystems. The Swiss water protection legislation stipulates that industrial wastewater must be treated to avoid water pollution insofar as this is technically possible and economically feasible [29]. Therefore, our results show that the measures currently taken by industries to avoid water pollution are not sufficient and additional actions should be assessed.

NDMA, NDEA, NDBA and NMOR were the only N-nitrosamines detected in the industrial effluents. It is likely that N-nitrosamines precursors other than dimethylamine, diethylamine, dibutylamine and morpholine are also present and may give rise to the formation of so far unidentified N-nitrosamines.

Industrial discharges are usually released either into municipal wastewater or directly into surface waters such as rivers or lakes. Although very high concentrations of N-nitrosamine have been detected in industrial discharges, dilution, photodegradation and biodegradation processes in municipal wastewater and/or surface water should significantly reduce their concentrations and hence the cancer risk level and potentially other effects. Nevertheless, because there is only limited information on long-term effects on aquatic organisms, the precautionary principle compels us to minimize the release of N-nitrosamines to the environment as much as possible. UV treatment of industrial effluents containing high N-nitrosamines concentrations could contribute to this objective but only in water with high UV-C light transmission.

Controlling industrial processes that are likely to form N-nitrosamines could reduce their discharges to municipal wastewater and the aquatic environment at the source. However, limited information is available on the industrial processes and mechanisms involved in the formation of N-nitrosamines present in industrial effluents. Moreover, more information is needed to detect potentially unidentified N-nitrosamines discharged by industrial wastewater.

Environmental implication

N-nitrosamines are an important group of potent human carcinogens and mutagens that can be present in water and wastewater. The concentrations measured in industrial wastewaters in Switzerland are orders of magnitude higher than those typically measured in municipal wastewater effluents. These results suggest that industrial effluents may be a major source of N-nitrosamines and responsible for the concentration peaks sometimes measured in some municipal wastewaters. As there is little information on long-term effects of N-nitrosamines on aquatic organisms, the release of high N-nitrosamines concentrations to the environment should be avoided as much as possible and industrial
wastewaters could be a good mitigation point.

CRediT authorship contribution statement

Florian Breider: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Funding acquisition. Carolline Gachet Aquillon: Resources, Methodology, Validation, Formal analysis, Writing – review & editing. Urs von Gunten: Conceptualization, Investigation, Writing – review & editing, Funding acquisition.

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.

Data availability

Data will be made available on request.

Acknowledgements

We acknowledge the Swiss Federal Office for the Environment (grant Q294–1130) for the financial support of this study and the companies that provided samples.

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