

Reducing the Emission of X-Ray Contrast Agents to the Environment

Decentralized Collection of Urine Bags and Its Acceptance

X-ray contrast agents (XCAs) are increasingly polluting water. One way of effectively tackling the root of the problem is direct collection of patient urine. This requires gaining broad acceptance among patients and medical personnel.

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Abstract

Iodinated x-ray contrast agents (XCAs) are water-soluble and persistent; their use and the associated water pollution are on the rise. They are not sufficiently removed in sewage treatment plants. XCAs are administered in medical facilities and are excreted almost unchanged in patients' urine within 24 hours. These properties predestine the direct collection of patient urine. In Germany source- and application-oriented approaches, which require a broad acceptance among the relevant actors, are politically discussed as important columns of a holistic micro-pollutant strategy. The applicability of urine bags and their acceptance by patients and staff were examined in the pilot project *MindER*. 159 patients, roughly 20 to 25 percent of those addressed, took part in the survey. They assessed the measure mainly positively. The assessment of the staff was more sceptical. For a high level of acceptance among medical staff, it is important that the bags can be integrated into existing routines as simply as possible.

Keywords

acceptance surveys, hospitals, intervention, patients, radiology, trace substances, urine bag, wastewater, water pollution, X-ray contrast agents

Pharmaceuticals make up a significant proportion of the trace substances polluting surface waters and groundwater. Among those, x-ray contrast agents (XCAs) are the group with by far the highest concentrations in surface water bodies (Ebert and Hein 2013, Ebert et al. 2014). Relatively high concentrations can be detected in all parts of the aquatic environment including groundwater and drinking water due to their persistence, wide use, solubility, polarity and stability. From 2003 to 2012, the consumption of XCAs in Germany has risen steadily from 352 tonnes per year to 454 tonnes per year, which is about three percent per year (LAWA 2016).

Figure 1 (p. 148) shows the estimated material flows of iodinated XCAs for Germany, assuming municipal wastewater treatment with nutrient elimination but without a fourth stage of purification¹ and a set-up with 80 percent outpatients and 20 percent inpatients. This scenario seems realistic based on the findings in the project *MindER* (*Minderung des Eintrags von Röntgenkontrastmitteln in die Umwelt – Reducing the emission of x-ray contrast agents to the environment*) which constitutes the basis for this study.

For example, near Karlsruhe, XCA emissions into the Rhine are estimated at more than six tonnes per year (UM Baden-Württemberg and LUBW 2014). This load increases continuously from

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¹ The fourth purification stage has been introduced so far only at a few wastewater treatment plants of size class 5 (> 100,000 population equivalent).

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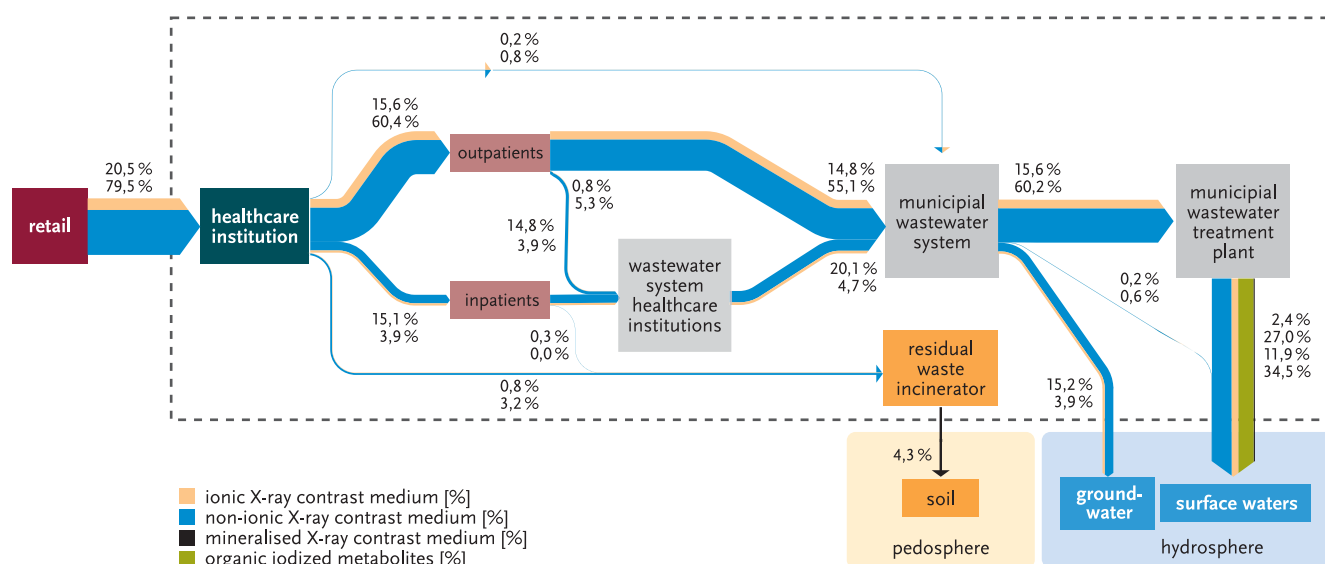


FIGURE 1: Material flows for iodinated x-ray contrast agents (XCAs) in Germany. XCAs are reduced through metabolic processes during wastewater treatment. In the end, about 45 percent of XCAs (ionic and non-ionic) are still released unchanged into the surface waters (based on data in Teschner 2015).

the Upper Rhine to its estuary (IKSR 2010). Ecotoxicological relevance of iodinated XCAs is not yet demonstrated. Sub-chronic and chronic animal experiments are missing. Critically to assess is that the chlorination of drinking water can convert, for example, the XCA Iopamidol into geno- and cytotoxically effective transformation products (LAWA 2016).

About 20 to 30 percent of the XCAs used are based on the rare earth element gadolinium (Gd) (Lindner 2017). Anthropogenic Gd from XCAs is found in ground- and tap water of bigger cities (Tepe et al. 2014). Like other XCAs Gd compounds are hardly removed in wastewater treatment plants and thus transferred to surface water. They reach the groundwater wells of waterworks through bank filtration (Kulaksiz and Bau 2011). Gd is suspected to release from the XCA complex and retain in organs such as brain bones and skin. Adverse health effects of Gd retention relate to a rare condition called nephrogenic systemic fibrosis (FDA 2015).

A large number of mainly technical research and pilot projects on eliminating micropollutants from municipal wastewater have been conducted over the past years (cp. Hillenbrand et al. 2015). A wide range of micropollutants can be removed from wastewater to a relatively large extent using fourth purification stage processes (ozone and activated carbon). While these are easily integrated into the existing purification process of a treatment plant, they cannot be regarded as the only solution. According to IKSR (2010) a fourth purification stage is less efficient at removing XCAs than it is for many other micropollutants: activated carbon often only removes XCAs moderately to poorly; the use of ozonation results in transformation products that may also be problematic in water.

XCAs are administered exclusively in specialized medical centers and are excreted with the urine almost completely within about

24 hours after use (Schuster et al. 2006). These properties facilitate the applicability of a decentral collection. Currently in Germany, such preventive source- and application-oriented approaches are considered as important columns of a holistic micropollutant strategy and are subject of political discussions (BMUB and UBA 2017). The implementation of the measures requires active support. It is therefore important to achieve a high acceptance among the relevant actors, in this case medical staff and the patients. Huijts et al. (2012, p. 526) have defined acceptance of a new technology as “behaviour that enables or promotes (support) the use of a technology, rather than inhibits or demotes (resistance) the use of it”. In *MindER*, urine bags were used as a decentral measure to collect contaminated urine. An alternative approach is the separate collection of urine with toilets and urinals, which is the focus of the follow-up project *MindER2*.

The urine bags contain a super absorber, which transforms the urine into a solid gel. They can be disposed via the residual waste in those areas where nonrecycled residuals are incinerated. In Germany, more than 95 percent of the municipal waste that cannot be recycled is incinerated (Pomberger et al. 2017). At present, thermal incineration is considered the safest way to dispose XCAs in an environmentally compatible way. To evaluate usability (in the sense of practicability and ease of use) of the measure and acceptance among the relevant actors, evaluating surveys formed an integral part of *MindER*. It thereby aims to close a research gap. Three earlier studies considered decentralized collection schemes for XCAs, partly including practical implementation, but lacking a very fine-grained analysis of acceptance and usability. Moreover, the sample size of approached patients was relatively small. In the first study, mobile containers (no urine bags) were issued to about 180 volunteer patients in the Charité Hospital in Berlin, who were asked to collect their urine separately for approximately 24 hours

(Pineau et al. 2005, Schuster et al. 2006). Almost 50 of those patients participated in the accompanying acceptance study. Stemplewski et al. (2015) tested urine bags in Gelsenkirchen. 30 percent of the 62 patients addressed participated and 89 percent of those thought the bags were easy to use. The third study compared various measures (ozonation, hospital sewage treatment plant, vacuum toilets and urine bags) purely on paper for the Swiss cantonal hospital in Liestal (BAFU 2009). Urine bags came out on top in terms of both the eliminated load and the cost-benefit ratio.

Pilot Project *Minder*

Minder focused on an extensive acceptance survey of the decentralized collection with urine bags. Core component was a pilot study, carried out in the second half of 2015 at two relatively large medical facilities in Ulm, Germany.² The aim of the intervention study was to analyze the feasibility of using urine bags as means of decentralized collection of urine with XCAs. The employed surveys focused on the usability of the urine bags as well as on the acceptance of the measure. It is likely that the usability of the urine bags also influences the acceptance of the measure. Two survey studies supplemented the pilot study: a psychological survey focused on intention, knowledge and awareness of the problem. It was not integrated into the pilot study to keep the questionnaire lengths reasonable. The other survey focused on utilization and disposal practices in radiological practices.

Pilot Study

Main elements of the pilot study were tailored questionnaires distributed to both patients and staff as well as a workshop and interviews. To attract publicity, the project was launched at a press conference attended by Ulm's mayor.

Procedure

As the medical personnel play a major role in implementing the pilot study, the *Minder* project team gave training, introduced the topic itself and made recommendations how to integrate the conduction of the pilot study into the staff's daily work routine. The pilot study was timed so that theoretically about 1,000 patients could be addressed. It was left up to the medical staff to decide which patients to approach to participate in the study. The addressed patients received a project flyer with information about the study's background and objectives, an information sheet with a summary and overview of the individual stages, a patient survey, seven urine bags (figure 2) and a postcard with final questions (including a prepaid return envelope).

The information material was given to the patient prior to the radiological examination. After the examination, the medical staff handed over the first urine bag that should be used on site for the first visit to the toilet. Subsequently, the patient answered the questionnaire while waiting for the images to be processed. The six remaining urine bags should be used at home in the 24 hours following the examination. Afterwards, the patient should complete



FIGURE 2: Urine bag – example as used in *Minder*.

the postcard with the final questions on use, usability and acceptance and sent it back.

Patient and Staff Questionnaires

To make participation easier, the design of the questionnaires was as short and simple as possible. The main topics surveyed in the patient questionnaire were chosen pragmatically: the practicability of the urine bag, evaluation of the information material, the perceived effectiveness of urine collection using bags as well as the acceptance and readiness to support widespread implementation of the scheme. In addition, sociodemographic characteristics and the patient's degree of mobility were surveyed.

The staff questionnaire aimed at surveying the acceptance and evaluation of urine collection from the viewpoint of the medical personnel. It included questions on the practicability of the urine bag for mobile and nonmobile patients,³ the evaluation of the training and information materials, estimation of the extra time required, and on how staff perceived the feasibility of integrating such routines into their daily work routines. It also addressed

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³ We distinguish between mobile and nonmobile as well as in- and outpatients. The first distinction refers to the patients' ability to use the toilet on their own. The latter refers to whether patients go home after the examination or not.

FIGURE 3: Evaluation after using the first urine bag (patients).

the perceived effectiveness, estimated acceptance among patients and staff's own acceptance and support of such a scheme. The staff completed the questionnaire at the end of the pilot study. In final interviews with the medical staff and a closing workshop with staff and patients, the experiences gained were explored in more depth.

Supplementary Surveys

Survey on Intention to Use

The psychological survey was conducted in two additional medical facilities, which had not participated in the pilot study.⁴ Thus, patients and staff did not receive any additional material other than the project flyer and a questionnaire. A urine bag was available for inspection.

The completion of the survey took place on-site.

The questionnaire focused on the intention to use urine bags as an intervention to protect the environment. The survey design was guided by the theory of planned behavior (Ajzen 1991). It included items capturing the knowledge about the topic and awareness of the problem, the former having implications for potential information campaigns, the latter because problem awareness is known to have an impact on actual behavior (e.g., Frick et al. 2004).

Survey on Utilization and Disposal Practices

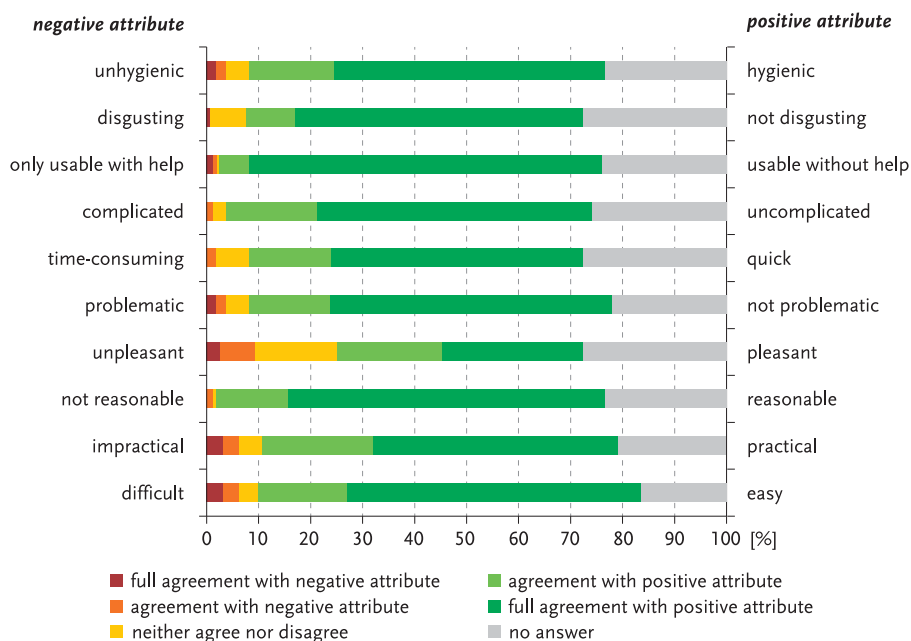
The *MindER* project team sent a written survey focusing on the status quo of utilization and disposal practices to almost 200 radiological facilities in Baden-Württemberg. It contained questions about the quantities and disposal of periodic XCA residues as well as the practical implementation of possible additional and alternative measures of urine collection.

Evaluations

Pilot Study

Patients' Participation and Characteristics

Contrary to the initial objective of including both out- and inpatients in the study, exclusively outpatients (approximately 80 percent of all XCA patients) were addressed in the hospital, because medical staff said they lacked the time and capacity to include usually nonmobile inpatients. Some of the outpatients were not addressed either because of their physical or mental state or because of language barriers. In total, the medical staff asked approximately 60 to 70 percent ($n = 600$ to 700 patients) of all XCA patients examined during the study period to participate in the study; participation was voluntary. Based on this information and the esti-



mated total number of patients, the response rate for the questionnaires is estimated at about 20 to 25 percent of the approached patients.

In total, 159 patients completed the accompanying questionnaire; slightly more than half of them are women (60 percent),⁵ the average age is around 60. The majority are between 45 and 74 years old. While the participation rate is relatively low, the absolute number of participants is higher than in comparable studies. We expect that the decision to participate is not random. Most likely, the sample composition is biased, containing more people who are in general more positive towards the intervention. Therefore, the results of the survey should not be generalized towards all patients but should be interpreted as being representative for a certain share of patients.

Patient Questionnaire Directly after the Examination

The first block of questions dealt with the experiences of using the urine bag, including their usability. Patients were asked to rate the question "For me, using the urine bag is ..." for ten pairs of attributes on a 5-point scale using semantic differentials (cp. Ajzen and Fishbein 1980). The list of attributes was developed in the context of *MindER*. The results are illustrated in figure 3. The display ranges from red bars (full agreement with the negative attribute shown on the left-hand axis) to dark green bars (full agreement with the positive attribute shown on the right-hand axis). On average, 28 percent of all ten pairs of attributes were not evaluated (gray

4 The intention survey took place in the German Army hospital, Ulm, and in the Radiology practice, City Plaza, Stuttgart. It was conducted by students of Business Psychology, University of Applied Sciences Darmstadt, in cooperation with Fraunhofer ISI.

5 This refers to the 93 percent respondents.

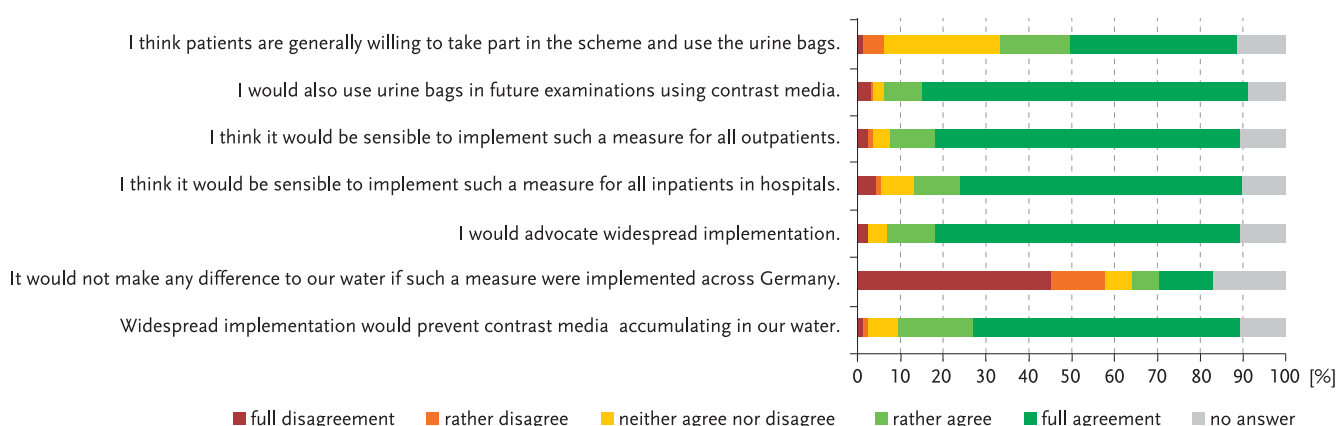


FIGURE 4: Results of patient questionnaire directly after examination – acceptance and effectiveness of using urine bags.

area in figure 3), because the participants often only answered parts of the questions. Only six percent of the 159 participants did not evaluate any of the attribute pairs.

The evaluations were very similar and mostly on the positive side of the scale. Participating patients assessed the use and usability of the urine bag very positively across all the pairs of attributes (between 47 percent and 74 percent of those questioned) except for the attribute pair “pleasant-unpleasant”. Although less favourably evaluated, 47 percent of the participants still selected the positive side of the scale here and 15 percent the middle. The largest complete agreement was accorded the statement that the urine bags can be used without help, followed by the statement that their use is not unreasonable.

On average across all the attribute pairs, the most positive category was selected in 61 percent of cases (corresponds to 69 percent of all the answered attribute pairs). The most negative response was chosen in 1.68 percent of cases on average (1.9 percent of all answered questions).

The second block of questions concerned the perceived effectiveness and acceptance of the measure (figure 4). The participants in the pilot study indicated a generally high level of willingness to collect urine using bags at future examinations with XCAs (complete agreement: 76 percent of respondents). The willingness of all XCA patients, in contrast, was estimated as much lower. The majority of participants approved widespread implementation for both outpatients (full agreement: 71 percent of respondents) and inpatients (full agreement: 66 percent of respondents). The perceived effectiveness of urine collection to reduce XCAs in water was generally high. The illustrated distribution of answers suggests that acceptance of the measure is very high among the patients who took part in the study.

Respondents’ comments mainly referred to the design of the urine bag and concerns about the waste produced due to using the bags.

Patient Questionnaire after One Day via Postcard

The reply postcard featured a first block of questions about the actual usage of the urine bag. Two questions assessed the patient’s

own and the general willingness to use urine bags and seven questions evaluated the usability of the urine bags. The response rate was just over 65 percent of the respondents to the first survey (n = 108).

On average, the participants used 5.4 urine bags. More than 80 percent stated that they had managed with the six urine bags provided; almost 17 percent would have needed additional bags (2.7 on average). The periods of use were particularly high for utilization up to four hours and at 21 to 24 hours. More than half the patients used the urine bags over the period of half a day or longer, 85 percent stated they used a urine bag every time they went to the toilet (figure 5). In the workshop, patients added that using the bag at night was perceived as annoying or as more difficult.

The patients who returned the postcard gave a mainly positive evaluation of the use of urine bags across all pairs of adjectives. Again, the most negative evaluation was for the perception of how pleasant it was to use. The largest complete agreement was once again for the statement that the urine bags can be used without

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FIGURE 5: Utilization period of urine bags.

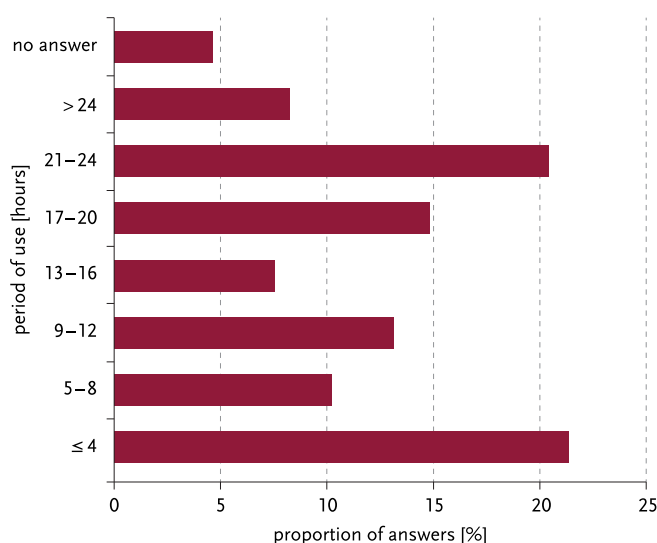


FIGURE 6: Evaluation of using urine bags for mobile patients (medical staff). In general, the medical staffs' evaluation is more critical than the responses of the participating patients (figure 3) because of the staffs' experiences with all the patients approached.

help. The majority of responses – similar to the first questionnaire – were in the positive range of the scale.

Staff Questionnaire

The staff questionnaires surveyed the use of urine bags from the viewpoint of the medical personnel. The same ten attribute pairs used in the patient survey were evaluated separately for mobile and nonmobile patients.

The medical staff assessed the handling of the bags more negatively than the participating patients (figure 6). The answers are plausible as the evaluation of the staff also considers the experienced willingness to participate of all patients including the majority of patients with a negative attitude towards the intervention.

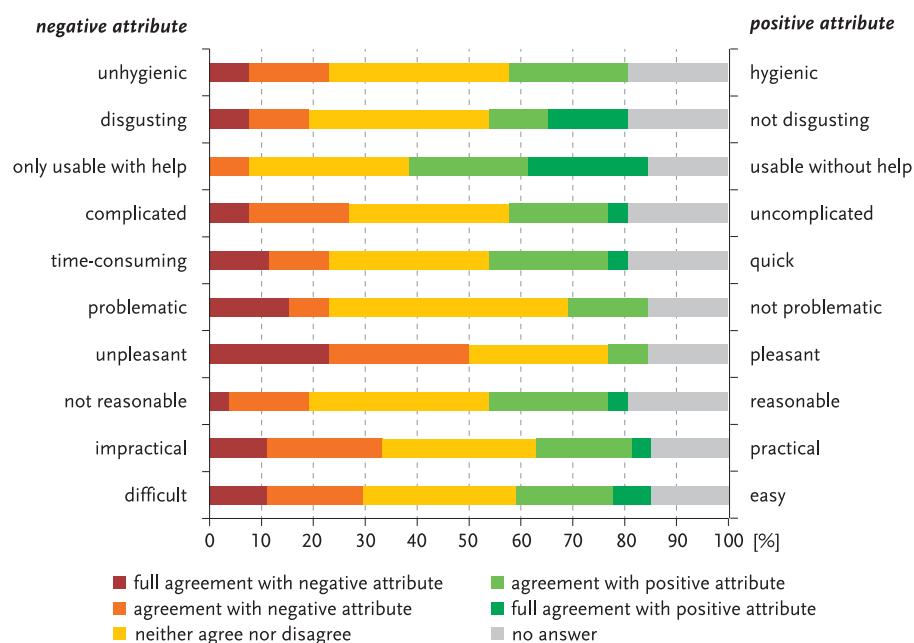
Analogous to the patients' results, the negative attribute in the pair “unpleasant – pleasant” received the comparatively largest consensus, “urine bags can be used without help” received the biggest positive consensus. “Undecided” was selected relatively often across all the attribute pairs (on average just over 20 percent).

The estimation for nonmobile patients was much more negative. There was almost always at least 50 percent agreement with the negative attribute; the exceptions were the attribute pairs “unhygienic – hygienic” and “disgusting – not disgusting”, each with about 30 percent consensus, and “unreasonable – reasonable” with just under 50 percent agreement.

With 83 percent, a large majority of the medical personnel presumed that using urine bags is in principle easier for men than for women; the rest did not expect any difference.

The staff also evaluated a more widespread implementation (figure 7). Whereas the effectiveness of the measure was perceived relatively positively (cp. agreement with the statement that widespread implementation of the scheme would be suitable to prevent the accumulation of contrast agents in water), its integration into the working day was judged very critically. There was also a relatively low assessment of the patients' willingness to participate.

The ease of integration into daily work routines depends strongly on the time needed. The median of the assessed required time per patient was around five (mean: 6.4) minutes for the individual staff member and ten (mean: 12.1) minutes for the team. Various elements would be omitted if the scheme was implemented as common practice or even as a mandatory measure, however, this was not expected to save much time. Figure 8 illustrates the perceived causes of the workload.



The biggest workload resulted from explaining things to the patients. Issuing the questionnaires was not seen as causing a lot of work; this explains why estimations of the amount of time for actually implementing the scheme (without the study) were not much lower. Coordination with colleagues was considered the least relevant for the time required.

Costs of the Measure

To evaluate a measure, the cost-effectiveness is important. The urine bags used in *MindER* cost 1.16 euros each. The majority of patients got along with six bags, resulting in direct cost of 6.96 euros per patient. The amount of applied XCAs varies over patients with an average of about 90 grams per examination (Rendl and Saller 2001, Pineau et al. 2005, Mestre et al. 2014). In contrast to technologies involving high fixed costs, the related costs when using urine bags only depend on the number of patients and result in about 78 euros per retained kilogram XCA. These considerations do not yet take into account the disposal of the bags or the increased personnel expenditure.

A comparison with the costs of the fourth purification stage in wastewater treatment plants has to consider the diversity and the width of the target substances, which is not the focus of this article. Literature indicates that urine bags are a relatively cost efficient measure (cp. BAFU 2009).

Supplementary Surveys

Survey on Intention to Use

159 patients and 44 medical personnel completed this survey.⁶ Participation was voluntary and thereby the sample composition is likely to be biased; results for a representative population might differ. In the following both groups will be analyzed subsequently, starting with the patients' responses. Based on a factor analy-

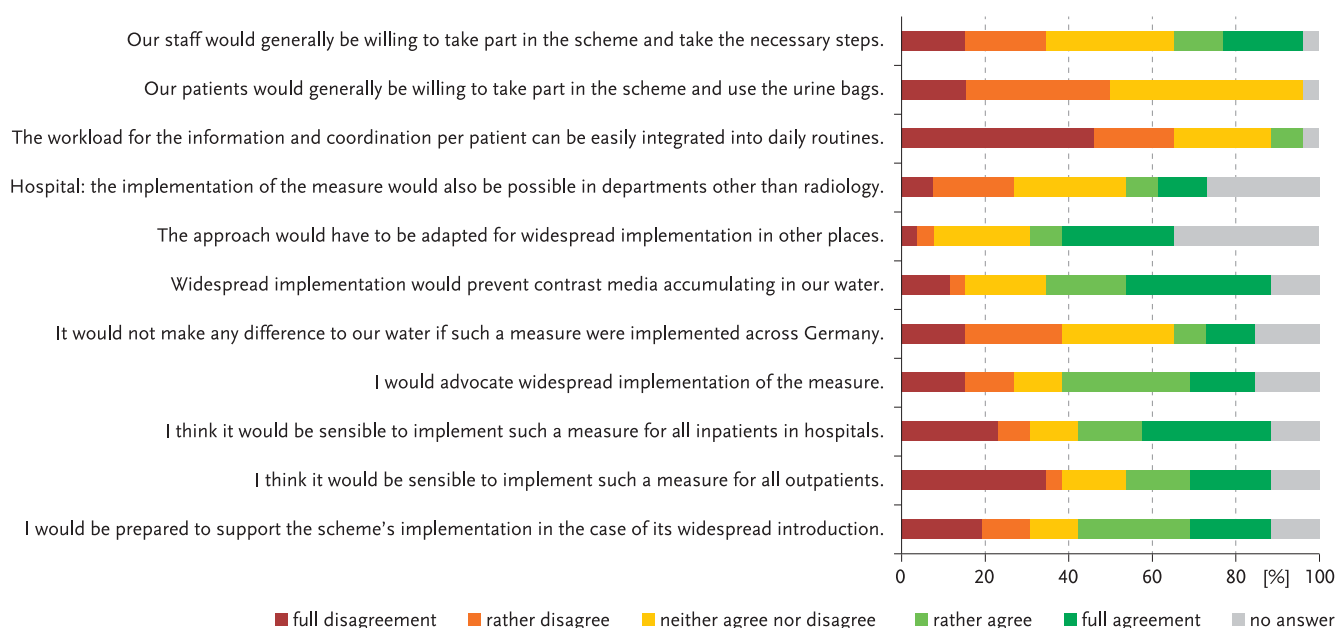


FIGURE 7: Perceived effectiveness, acceptance and support of the scheme (medical staff). Like the participating patients (figure 4), medical staff evaluated the effectiveness as good, but was more sceptical with regard to implementation and acceptance.

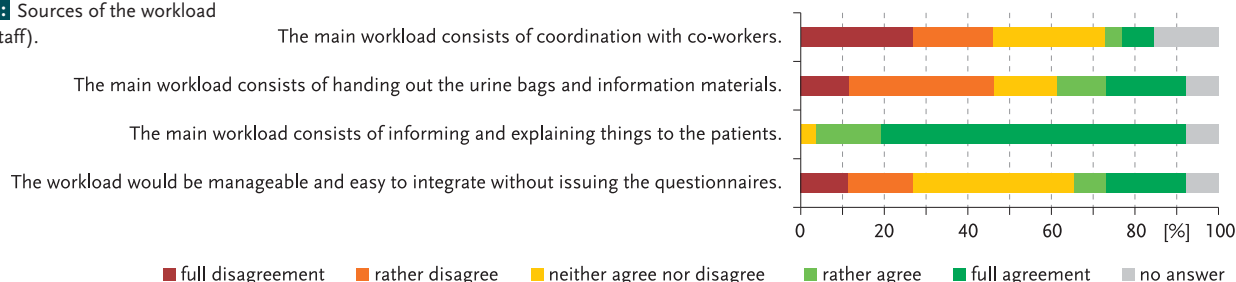
sis, five factors were identified relating to the three components of the theory of planned behavior. A regression of the behavioral intention index on those five factors reveals that except for one (SN_for_others)⁷, all factors exhibit a significant effect (table 1, p. 154): among the two factors relating to component 1 *subjective norm* (SN) (expression of the individually perceived social pressure), the perceived expectations of relevant persons (e.g., family or doctor), significantly and positively influence the willingness to use a urine bag (SN_relevant_persons). Own expectations on other people's behavior show no impact (SN_for_others). Component 2 *attitude* loads on two factors, one relating to a general attitude (attitude_general) and one relating to the personal implications of the specific implementation (attitude_implication). Both are positive; thus, the intention to use a urine bag increases the more positive the attitude is. The last component, the *perceived behavioral control* (PBC), also has a positive impact on the behavioral intention index: the simpler the perceived use of the urine bag, and the more the use itself is regarded as an effective way to reduce the emission of XCAs to water, the higher the willingness to use it.

The majority of the participants are prepared to use a urine bag after an examination. Roughly, half of the patients expect that they would be encouraged to use urine bags by those around them and their doctor. A quarter of the participants think they are difficult to use. Comments made by participants suggest that acceptance is closely linked to the general attitude towards environmental issues.

The staff answers concerning the willingness to support the scheme are more heterogeneous. Answers about whether staff would recommend the use of urine bags were spread equally across yes, no or neutral. Similar results emerge with regard to the expected support of the measure by superiors and the additional time required. The main expected problems are the time needed for, possibly required, support when using urine bags and for the

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FIGURE 8: Sources of the workload (medical staff).



6 The number of participants and the reported n in the subsequent regressions differ slightly due to partially missing responses.

7 This item relates to the statement "I do not think other patients would be willing to use urine bags".

TABLE 1: Linear regression of patient responses on the behavioral intention index on all identified factors ($n=148$, β =standardized regression coefficient, $*p < .05$, Source: Bicker et al. 2016). The five factors relate to *subjective norm* (SN), *attitude* and *perceived behavioral control* (PBC). All factors except the own expectations on other people's behavior (SN_for_others) have a significant impact on the willingness to use urine bags.

INDEX	β	95 % CONFIDENCE INTERVAL
SN_relevant_persons	0,333*	[0,281; 0,598]
SN_for_others	-0,031	[-0,144; 0,071]
attitude_implication	0,155*	[0,043; 0,338]
attitude_general	0,232*	[0,111; 0,420]
PBC	0,300*	[0,203; 0,670]

collection and a possibly required disposal. Note that in this context the generalizability of the results is limited due to the small sample size. It is unclear whether systematic differences are to be expected.

Like above, the answers of the medical personnel load on five factors associated to the theory of planned behavior. The expressed willingness of personnel to support the scheme increases with the perceived ease of implementation (PBC_implementation) and estimated preventive effectiveness of the measure (PBC_expected_outcome). For none of the other identified factors a significant relation can be observed from the regression (table 2). Among the other factors, two factors are associated with the *subjective norm*, one relating to the prevention aspect (SN_prevention), one relating to the norm among colleagues (SN_colleague). Finally, *attitude* loads on one single factor (attitude).

Survey on Utilization and Disposal Practices

The motivation for this survey was the learning that a common disposal practice for the residues of XCAs left over every evening is to empty the contents down the drain to be able to dispose the glass bottle in recycling containers. A short questionnaire was developed to better estimate the quantities involved and therefore the significance. 189 radiological practices were contacted of which about 15 percent ($n=29$) returned the survey.

According to the respondents, on average, about 40 milliliters XCA are left over in each facility every day that have to be disposed of because they are not allowed to be used the following day for reasons of hygiene. There are basically three main ways to dispose of the bottles or bottles containing residues that are used with equal frequency: complete disposal via residual waste, complete disposal via glass recycling and separate disposal via wastewater and glass recycling.

Conclusions

The objective of *MindER* was to use acceptance and usability studies to evaluate the options and effectiveness of using urine bags to reduce the emission of XCAs to the environment.

TABLE 2: Linear regression of staff responses on the behavioral intention index on all identified factors ($n=39$, β =standardized regression coefficient, $*p < .05$, Source: Bicker et al. 2016). The five factors relate to *subjective norm* (SN), *attitude* and *perceived behavioral control* (PBC). Only the two factors relating to PBC – the estimated preventive effectiveness of the measure and the perceived ease of implementation – have a significant effect on the willingness of personnel to support the scheme.

INDEX	β	95 % CONFIDENCE INTERVAL
SN_prevention	0,093	[-0,115; 0,317]
SN_colleague	-0,017	[-0,429; 0,372]
attitude	-0,192	[-0,795; 0,278]
PBC_expected_outcome	0,548*	[0,242; 0,989]
PBC_implementation	0,642*	[0,378; 1,087]

The participating patients gave a very positive evaluation of the scheme and showed high acceptance of its widespread implementation. In particular, the large majority of the participants evaluated the usability of urine bags positively. More than 75 percent agree to use the measure in future applications. However, only about 20 to 25 percent of patients participated in the study under the given conditions. It is likely that the general acceptance level is lower than the answers of the respondents suggest.

Correspondingly, the medical personnel estimated a lower general acceptance of patients and showed more restrained willingness towards implementation. This may also be due to the fact that staff expects an increase in the workload, resulting in particular from informing patients and explaining the procedure. When implemented into the standard routines with less voluntary character, it can be expected that the participation rate is higher than in this pilot study.

The results of the accompanying surveys indicate that, from the viewpoint of both patients and staff, an important prerequisite is the ease of implementing the measure. Good information and communication seem vital here to convey the benefits and effectiveness of such a scheme successfully. For the patients' willingness, it seems relevant that the medical personnel support the scheme and communicate it as standard procedure.

In principle, there is a clear need for action to reduce the discharge of XCAs into water due to its increasing consumption and its now ubiquitous presence in the aquatic environment. There are various options available here including source-based, decentralized and end-of-pipe measures that are effective for XCAs up to a certain point. One of those measures, the relatively cost efficient collection in urine bags, was tested in this study. These bags are practicable and acceptable for a certain share of patients and can therefore be suggested as one important element among other complementary measures in a strategic approach against pharmaceuticals in the environment on EU or national level. Policy requirements are necessary for broad implementation including a clear allocation of the costs. Evaluating the costs and benefits of possible combinations of measures is a question for further research.

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