Health risk-based prioritization approaches of pharmaceuticals in the Upper Citarum River Basin

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Abstract. Two methods were developed to prioritize human health risks of pharmaceuticals based on defined daily doses (DDDs) obtained from the WHO and acute toxicity data on pharmaceuticals (TDLo) obtained from the PubChem database. A major advantage of these methods is that it requires no acceptable daily intake (ADI), reference dose (RfD), or tolerable daily intake (TDI) values, which are often unavailable or difficult to obtain for pharmaceuticals group. Both methods were applied to prioritize 16 pharmaceuticals detected by passive samplers in the water source of Ciwalengke Village, a peri-urban area in the Upper Citarum River Basin. Ten out of 16 pharmaceuticals could be prioritized by using both methods. The risk indicator values (RIhum) showed good agreement between the two approaches, especially for Caffeine and Trimethoprim. The priority ranking of Caffeine and Lidocaine were always in the top 3 highest human health risks. The ranking comparison showed considerable consistency, indicating that both prioritization methods are reasonably in line with each other. The pharmaceutical intake through the exposure of contaminated river water was expected to pose negligible human health risks (i.e. RIhum < 1) but can be refined more by conducting supplementary effects studies for other individual pharmaceuticals or pharmaceuticals mixtures.

Keywords: DDD; HRV; Pharmaceuticals; Prioritization; Health Risk; TDLo.

1. Introduction
Pharmaceuticals are used to prevent and treat animal and human diseases. After use, pharmaceuticals and their metabolites can be released to the environment, e.g. through excretion and emission into sewerage systems, from aquaculture and meadow livestock, or application of manure to agriculture [1]. The pharmaceuticals that are discharged to water can cause adverse effects for aquatic ecosystems [2, 3, 4, 5, 6] and human health [7, 8, 9, 10, 11]. Not all impacts are directly visible and observable; some impacts are difficult to detect, such as delayed and subtle effects (e.g. behavioural changes, chronic
effect, bioaccumulation, etc.) [12, 13, 4, 2, 14, 64, 65]. One of the major challenges for risk assessment of pharmaceuticals is that information on potential adverse impacts of pharmaceuticals in water is still limited [15]. This is partially due to the fact that toxicity testing of pharmaceuticals is time-consuming, complicated and expensive [16]. Moreover, there are more than 1500 active pharmaceutical ingredients (APIs) being used by society, some in substantial quantities [60]. It is therefore hardly surprising that APIs and their major metabolites frequently appear in the surface waters around the globe [17, 61]. To deal with this myriad of APIs and metabolites, prioritization approaches are needed to reduce the number of pharmaceuticals to be studied in order to identify and focus on pharmaceuticals that are likely to pose the greatest risk [18, 19, 16].

Several pharmaceutical prioritization methods have been applied around the world [20, 16, 21, 22, 23, 62]. A study of risk prioritization assessed 99 pharmaceuticals in cities of Iraq (i.e. Basrah, Mosul, Baghdad). The result revealed that only analgesics, antidepressants, and antibiotics groups which had high risk for aquatic and terrestrial ecosystem [20]. Another study showed 67 pharmaceuticals and personal care products (PPCPs) were detected in the effluent from municipal wastewater treatment plants of Beijing. A risk prioritization scenario was applied and 17 PPCPs were classified as high risk priority with the highest risk were ofloxacin, 17α-ethynylestradiol, dibutyl phthalate, diocetyl phthalate, and sulfamethoxazole [23]. Most prioritization studies indicated that less than 10 compounds had high risk [24]. It signified that only a restricted number of pharmaceuticals cause the major part of the risk. However, these prioritizations only assessed the risk for aquatic ecosystems. In some Indonesian areas, river water is still being used as a water source for daily domestic activities and drinking water [25, 26, 27]. Therefore, prioritization based on human health risk is crucial for appropriate risk management of river basins where the communities are dependent on the use of river water, like in Indonesia.

Health risk-based prioritization approaches require health-based reference values (HRVs) such as the tolerable daily intake (TDI), acceptable daily intake (ADI), or reference dose (RfD) [28, 29, 19, 30]. Pharmaceuticals prioritization can be particularly challenging because HRVs are often lacking. In order to overcome limited availability of HRVs, this study proposes two methods to prioritize pharmaceuticals in the absence of HRVs, i.e. based on defined daily dose (DDD) and based on acute toxicity data. These methods may be used by the authorities in proposing suitable mitigation and/or monitoring measures for health protection in connection with pharmaceuticals contamination in surface water. The prioritization approaches were applied in a tributary of the Citarum River in Ciwalengke Village, Upper Citarum River Basin, where the residents still use river water as their main water source for domestic activities and drinking water [31, 32, 33, 34].

2. Materials and method
The procedure of human health risk-based prioritization for pharmaceuticals is illustrated in figure 1. The prioritization was based on a non-dimensional indicator of human health risk (RIhum) that was estimated for each substance individually using the equation (1) below:

\[
RI_{hum} = \frac{CDI}{HRV}
\]

where CDI is the estimated chronic daily intake (mg/kg/day), and HRV is the health-based reference value (mg/kg/day). The HRVs used in the present study were derived using two methods, i.e.:

a. HRVs were derived from the therapeutic concentration/oral dosing. It was assumed that for most pharmaceuticals no toxic effects will occur at the normal dosing regimen. The normal dosing has been defined by the World Health Organisation in the Defined Daily Dose (DDD). A safety factor of 1000 was applied to derive an HRV from the DDD.

b. HRVs were derived from acute toxicity data (TDLo) obtained from the PubChem database. Assuming all Toxic Dose Low (TDLo) values had the same exposure duration, the lowest TDLo value was used as HRV after division by an assessment factor of 1000.

The CDI value (mg/kg/day) value was calculated with the assumption that the river water was directly ingested as drinking water and by implementing the following equation (2):
\[ CDI = \frac{C \times IR}{BW} \]  

(2)

C is the pharmaceuticals concentration (mg/L) in the surface water (obtained by passive sampling); IR is the ingestion rate (with the assumption of 2 L/day); also BW as the body weight (assumed to equal 60 kg for adults; [38]).

\textbf{Figure 1.} Diagram of pharmaceuticals health risk-based prioritization approaches.

Pharmaceutical concentrations were obtained by passive sampling. Passive sampling is a cost-efficient environmental monitoring technique for long-term on-site pollutant monitoring [39, 40, 41, 42, 43, 44]. The passive sampling technique and its methods had been subjected to extensive testing compared to traditional sampling [45, 46, 47, 48, 49].

We deployed two types of passive samplers, i.e. speedisk and silicon sheets, to cover the polar range of substances (hydrophobic-hydrophilic). Prior to field deployment, the silicon sheets were rinsed with performance-reference-compounds (PRCs) for estimating the sampling rate (L/d) and aqueous phase concentrations of pharmaceuticals in both speedisks and silicon sheets [50, 51]. After the period of sampling, the samplers were cleaned, cooled, and the active pharmaceutical ingredients were extracted and analyzed through gas chromatographic (GC) and high performance liquid chromatographic (HPLC).

In this study, we used similar sampling procedures and passive samplers analyses as described in Utami et al. (2020; [28]). The passive samplers were deployed for four weeks in the dry season (August 18th, 2016 – September 20th, 2016). For the deployment, three speedisks and six silicon sheets were linked on a iron bar and were kept immersed for the duration of sampling period. In spite of polar ranges differences, the concentration uptake of silicon and speedisk samplers might be partly overlaps. Each time the measurement produced two concentration values, we used the highest value as the input of risk prioritization procedure.

The passive samplers were deployed in two locations in Ciwalengke Village. The first one is in the water source inlet of the village and the second location is in the water channel in the middle of the village. Ciwalengke is a neighborhood located in Sukamaju Village of Majalaya District, Bandung Regency and included in the Upper Citarum River Basin (UCRB) area (7.0522° S, 107.7533° E; figure 2).
Ciwalengke Village covers an area of about 90 ha and is surrounded by factories and rice fields (figure 2). It is one of the slums in the UCRB with approximately 4000 inhabitants [33]. The lack of a clean water service system and the limited access to piped water causing the residents to use unprotected water sources from the irrigation channel, originating from a tributary of the Citarum River [31, 32]. This channel is contaminated with waste discharged by the surrounding industries [33, 34]. The water flows directly into the village through pipes and is stored in a tub and shallow well. The residents use the river water for their daily activities. The water does not fulfil the criteria of water source quality based on Indonesian Regulation [52, 53, 33, 54, 55].

3. Results and discussion

3.1 Pharmaceuticals HRV derivations

Sixteen pharmaceuticals were detected in the sampling area. The highest concentration was found for Lidocaine with 350 ng/L, followed by Caffeine and Ibprofen with 310 ng/L and 60.8 ng/L, respectively. The lowest concentration was found for Sulfadiazine with 0.3 ng/L. Table 1 lists the measured concentrations and the health-based reference values (HRVs) derived for the 16 pharmaceuticals using DDD values from WHO and acute toxicity data (TDLo values) from the PubChem Database.

Figure 2. Location of the passive sampler in the Ciwalengke Village.
From the WHO DDD values, 13 out of 16 pharmaceuticals could be processed to obtain HRVs. BPA, Cytarabine and Furazolidone did not have DDD values, so the HRVs could not be derived. From acute toxicity data from the PubChem Database, 11 out of 16 HRVs could be derived. BPA, Estrone, Furazolidone, Lincomycin, and Progesterone did not have a TDLo value.

No toxic effects are expected at the DDD. However, a safety factor of 1000 was applied because the DDD applies for short term exposure (e.g. 3-10 days in a row) while the human reference values such as the ADI, TDI and RF reflect a lifetime daily exposure. The height of the assessment factor does not affect the ranking of the drugs, but it does affect the absolute value of the risk indicator.

Whether an HRV should be derived from acute toxicity data obtained from literature (PubChem Database) is a matter of debate among risk assessors. In total, 250 acute toxicity data were extracted from the PubChem Database (i.e. LD50, LDLo, TDLo, EC50, LC50), but only TDLo values (56 data) were used since lethality was considered an inappropriate effect indicator for the present prioritization exercise. An assessment factor of 1000 was applied to reduce the uncertainty in the HRV.

In an exposure risk assessment, uncertainties can be present in the characterization of the exposure scenario, the parameter estimates, model predictions, etc [63]. To cover those uncertainties, we need to apply an assessment factor. If an assessment factor equals to or higher than 100 is used, it signifies a high level of uncertainty [37]. In this study we faced the uncertainty of pharmaceuticals toxicity data. Practically, the uncertainty of toxicity data in a substance could be reduced by performing additional toxicity tests for other species which can be quiet complicated and also time-consuming. Instead of doing that, this study assumed that the level of uncertainty of the detected pharmaceuticals were quiet high and use 1000 as single assessment factor value for all pharmaceuticals. This assumption was applied since only short term toxicity data were available for all measured pharmaceuticals in this study, irrespective of whether or not the species tested was a standard test organism. The use of a factor of

<table>
<thead>
<tr>
<th>Pharmaceuticals</th>
<th>CAS</th>
<th>Concentration (ng/L)</th>
<th>CDI (mg/kg.day)</th>
<th>HRVs (mg/kg/day)$^a$</th>
<th>DDD</th>
<th>TDLo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPA</td>
<td>80-05-7</td>
<td>45.00</td>
<td>1.5.E-06</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Caffeine</td>
<td>58-08-2</td>
<td>310.00</td>
<td>1.0.E-05</td>
<td>6.7.E-03</td>
<td>7.0.E-03</td>
<td></td>
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<tr>
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<td>56-75-7</td>
<td>22.69</td>
<td>7.6.E-07</td>
<td>5.0.E-02</td>
<td>2.5.E-02</td>
<td></td>
</tr>
<tr>
<td>Chloroquine</td>
<td>54-05-7</td>
<td>0.82</td>
<td>2.7.E-08</td>
<td>8.3.E-03</td>
<td>2.0.E-03</td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>147-94-4</td>
<td>2.88</td>
<td>9.6.E-08</td>
<td>NA</td>
<td>9.5.E-05</td>
<td></td>
</tr>
<tr>
<td>Estrone</td>
<td>53-16-7</td>
<td>18.00</td>
<td>6.0.E-07</td>
<td>1.7.E-05</td>
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<td>NA</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>67-45-8</td>
<td>0.62</td>
<td>2.1.E-08</td>
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<td>NA</td>
<td>NA</td>
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<tr>
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<td>51146-56-6</td>
<td>60.80</td>
<td>2.0.E-06</td>
<td>2.0.E-02</td>
<td>8.0.E-03</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
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<td>350.00</td>
<td>1.2.E-05</td>
<td>5.0.E-02</td>
<td>1.6.E-02</td>
<td></td>
</tr>
<tr>
<td>Lincomycin</td>
<td>154-21-2</td>
<td>7.85</td>
<td>2.6.E-07</td>
<td>3.0.E-02</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>103-90-2</td>
<td>38.93</td>
<td>1.3.E-06</td>
<td>5.0.E-02</td>
<td>5.0.E-03</td>
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</tr>
<tr>
<td>Progesterone</td>
<td>57-83-0</td>
<td>2.18</td>
<td>7.3.E-08</td>
<td>5.0.E-03</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>69-72-7</td>
<td>2.61</td>
<td>8.7.E-08</td>
<td>4.7.E-02</td>
<td>1.1.E-02</td>
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</tr>
<tr>
<td>Sulfadiazine</td>
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<td>0.30</td>
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<td>1.0.E-02</td>
<td>2.9.E-02</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
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<td>15.43</td>
<td>5.1.E-07</td>
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<td>1.6.E-02</td>
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</tr>
<tr>
<td>Trimethoprim</td>
<td>738-70-5</td>
<td>21.00</td>
<td>7.0.E-07</td>
<td>6.7.E-03</td>
<td>6.0.E-03</td>
<td></td>
</tr>
</tbody>
</table>

$^a$NA: Not Available
1000 on acute or short-term toxicity data is a protective and conservative factor and is intended to assure that pharmaceuticals with the potential to cause negative impacts are identified [36, 37]. Pharmaceuticals typically are biologically active compounds that interact with specific targets in the human body [64]. The effect triggered can be very specific and can be difficult to detect in a toxicity study, e.g. a behavioural change of an antidepressant [13, 14, 65]. As such, it is defendable to use a high assessment factor to extrapolate TDLo values to HRVs.

The methods proposed in the present study resulted in more HRVs than the common method of using ADIs, TDIs and RfDs. In total, HRVs could be derived for 14 out of 16 pharmaceuticals while only one HRV value is available when using ADIs, TDIs and RfDs, i.e. for BPA (RfD of 0.05 mg/kg/day from IRIS or TDI of 0.004 mg/kg/day from EFSA). Prioritization would have been impossible if it would have been based on HRVs from ADIs, TDIs and RfDs only.

### 3.2 Health risk prioritizations

Table 2 lists the results of the risk prioritization based on DDD data from the WHO and acute toxicity data (TDLo) extracted from PubChem. The first prioritization using DDD values shows that the highest risk rank was obtained for Estrone with a R_{hum-DDD} of 3.6.E-02 (1st), followed by Caffeine with a R_{hum-DDD} of 1.6.E-03 (2nd) and Lidocaine with a R_{hum-DDD} of 2.3.E-04 (3rd). The last risk rank or lowest R_{hum-DDD} value was Sulfadiazine with 9.9.E-07 (13th). Three out of 16 pharmaceuticals could not be prioritized because their HRVs could not be derived. From a total of 13 R_{hum-DDD} calculations, there was no R_{hum-DDD} value above 1, indicating negligible human health risks.

<table>
<thead>
<tr>
<th>Pharmaceuticals</th>
<th>CAS</th>
<th>DDD a</th>
<th>TDLo a</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RI_{hum}</td>
<td>Rank</td>
<td>RI_{hum}</td>
</tr>
<tr>
<td>Estrone</td>
<td>53-16-7</td>
<td>3.6.E-02</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Caffeine</td>
<td>58-08-2</td>
<td>1.6.E-03</td>
<td>2</td>
<td>1.5.E-03</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>137-58-6</td>
<td>2.3.E-04</td>
<td>3</td>
<td>7.3.E-04</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>738-70-5</td>
<td>1.1.E-04</td>
<td>4</td>
<td>1.2.E-04</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>51146-56-6</td>
<td>1.0.E-04</td>
<td>5</td>
<td>2.5.E-04</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>103-90-2</td>
<td>2.6.E-05</td>
<td>6</td>
<td>2.6.E-04</td>
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<tr>
<td>Sulfamethoxazole</td>
<td>723-46-6</td>
<td>1.5.E-05</td>
<td>7</td>
<td>3.2.E-05</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>56-75-7</td>
<td>1.5.E-05</td>
<td>8</td>
<td>3.0.E-05</td>
</tr>
<tr>
<td>Progesterone</td>
<td>57-83-0</td>
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<td>9</td>
<td>NA</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>154-21-2</td>
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<td>10</td>
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</tr>
<tr>
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<td>11</td>
<td>1.4.E-05</td>
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<td>Salicylic acid</td>
<td>69-72-7</td>
<td>1.8.E-06</td>
<td>12</td>
<td>7.8.E-06</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>147-94-4</td>
<td>NA</td>
<td>NA</td>
<td>1.0.E-03</td>
</tr>
<tr>
<td>BPA</td>
<td>80-05-7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>67-45-8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA: Not Available

The second prioritization approach was performed by using HRVs from TDLo data extracted from PubChem. The result showed that 11 out of the 16 pharmaceuticals could be prioritized. The first
risk rank was obtained by Caffeine with a $R_{I_{hum-TDLo}}$ of 1.5.E-03 (1st), followed by Cytarabine with a $R_{I_{hum-TDLo}}$ of 1.0.E-03 (2nd) and Lidocaine with a $R_{I_{hum-TDLo}}$ of 3.7.E-04 (3rd). The lowest $R_{I_{hum-TDLo}}$ value was Sulfadiazine with 3.4.E-07 (11th). Five pharmaceuticals could not be prioritized because of lacking HRVs. All risk indicators from 11 $R_{I_{hum-TDLo}}$ estimation were under 1, implying negligible human health risks.

3.3 Comparison between prioritization methods

Based on the prioritization results (table 2), 10 out of 16 pharmaceuticals could be prioritized by using DDD and TDLo methods, i.e. Caffeine, Lidocaine, Trimethoprim, Ibuprofen, Paracetamol, Sulfamethoxazole, Chloramphenicol, Chloroquine, Salicylic acid, and Sulfadiazine. In assessing the performance of prioritization approaches, the result of $R_{I_{hum-DDD}}$ were plotted against the $R_{I_{hum-TDLo}}$ values (figure 3). The graph consist of 10 dots, representing pharmaceuticals that could be prioritized by using both methods.

![Figure 3](image_url)

**Figure 3.** Comparison of $R_{I_{hum-DDD}}$ (x-axis) and $R_{I_{hum-TDLo}}$ (y-axis) of pharmaceuticals in the study location. The solid line indicates a 1:1 match between $R_{I_{hum-DDD}}$ and $R_{I_{hum-TDLo}}$, while the dashed lines indicate a ten-fold difference.

The solid line in figure 3 indicates a perfect match between two $R_{I_{hum}}$ values of a pharmaceutical. The dashed lines indicate a factor of 10 difference. The developed approaches performs relatively good from the comparison between $R_{I_{hum-DDD}}$ and $R_{I_{hum-TDLo}}$ values, especially for Caffeine and Trimethoprim (see figure 3). Both $R_{I_{hum}}$ values of Caffeine and Trimethoprim were very close to each other. Generally, the $R_{I_{hum-TDLo}}$ Values tend to be slightly higher than the $R_{I_{hum-DDD}}$ values for almost all pharmaceuticals, except for Caffeine and Sulfadiazine. Overall, $R_{I_{hum}}$ comparison of 10 pharmaceuticals were within a factor of 10, indicating that both methods produced resemble risk indicators. The ranking comparisons of 10 pharmaceuticals between two methods were shown in table 3.
Table 3. Comparison of health risk ranking of 10 pharmaceuticals between two prioritization methods.

<table>
<thead>
<tr>
<th>Pharmaceuticals</th>
<th>CAS</th>
<th>RHum-DDD</th>
<th>Rank-DDD</th>
<th>RHum-TDLo</th>
<th>Rank-TDLo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>58-08-2</td>
<td>1.6E-03</td>
<td>1</td>
<td>1.5E-03</td>
<td>1</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>137-58-6</td>
<td>2.3E-04</td>
<td>2</td>
<td>7.3E-04</td>
<td>2</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>738-70-5</td>
<td>1.1E-04</td>
<td>3</td>
<td>1.2E-04</td>
<td>5</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>51146-56-6</td>
<td>1.0E-04</td>
<td>4</td>
<td>2.5E-04</td>
<td>4</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>103-90-2</td>
<td>2.6E-05</td>
<td>5</td>
<td>2.6E-04</td>
<td>3</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>723-46-6</td>
<td>1.54E-05</td>
<td>6</td>
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<td>6</td>
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<tr>
<td>Chloramphenicol</td>
<td>56-75-7</td>
<td>1.51E-05</td>
<td>7</td>
<td>3.0E-05</td>
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</tr>
<tr>
<td>Chloroquine</td>
<td>54-05-7</td>
<td>3.3E-06</td>
<td>8</td>
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<tr>
<td>Salicylic acid</td>
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<td>9</td>
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<td>68-35-9</td>
<td>9.9E-07</td>
<td>10</td>
<td>3.4E-07</td>
<td>10</td>
</tr>
</tbody>
</table>

Comparing the results of both prioritization approaches (table 3), Caffeine and Lidocaine were the two pharmaceuticals that ranked in the top two of both methods. The rank differences between two methods were only found in Trimethoprim and Paracetamol. Overall, the comparison of the DDS and TDLo-based rankings shows considerable consistency in results, indicating that both prioritization methods are reasonably in line with each other.

All pharmaceuticals detected in the study area had risk indicator values under unity. It shows that the intake of the investigated individual pharmaceuticals with the consumption of Citarum River water causes negligible health risk. Nonetheless, it should be remembered that this study did not consider other exposure routes such as dermal exposure, inhalation exposure, or the consumption of contaminated fish. Furthermore, there might be potential interactions between pharmaceuticals that could lead to adverse effects [56, 57, 58]. For instance, a study by Denton et al (2003) showed that a combination of esfenvalerate and diazinon resulted in a toxic effect on larvae of Pimephales promelas, while no toxicity was observed when only esfenvalerate was given [59]. Therefore, caution is warranted when estimating toxicity of pharmaceutical mixtures in the water.

4. Conclusions
Two approaches of health risk-based prioritization were developed and applied to 16 pharmaceuticals detected by passive samplers in the water source of Ciwalengke Village in the UCRB. Each method produced 13 and 11 pharmaceutical HRVs respectively, while only one HRV could be derived when applying the common method by using ADI, TDI, or RfD value. This study has proven that the developed methods are able to overcome the limited availability of ADI, TDI, and RfD values in pharmaceuticals prioritization.

In total, 10 out of 16 pharmaceuticals could be prioritized by using both methods. The comparison between methods showed that risk indicator values of 10 pharmaceuticals were within a factor of 10, showing that both methods resulted resemble risk indicators. The prioritization results of both methods also showed considerable consistency in ranking with Caffeine and Lidocaine that were always in the top 3 highest risks, indicating that the risk prioritization approaches in this study are reasonably robust.

The risk indicators resulting from the pharmaceuticals intake from the Citarum River water were far below unity, implying negligible human health risks ($R_{hum} < 1$) for all individual pharmaceuticals toxicity. However, it should be remembered that we did not consider other exposure routes (e.g. dermal exposure, inhalation, dietary of contaminated fish, etc.) nor possible interactions between pharmaceuticals that might provoke adverse effects. The health risk-based prioritization methods in this study can be a beneficial tool for the authorities to determine which pharmaceuticals with the highest risk and increase the efficiency of risk assessment in the river basin.
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