A REVIEW OF THE EUROPEAN COMMISSION APPROACH TO ALLOCATING TOXIC LOAD TO HUMAN PHARMACEUTICALS IN URBAN WASTEWATER

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1 SUMMARY

At the request of EFPIA, RSA has undertaken an analysis of data used by the European Commission (the Commission) to calculate the 66% toxic load which it has attributed to pharmaceuticals as a basis for allocating costs under Extended Producer Responsibility (EPR) Schemes in accordance with the recast EU Urban Wastewater Treatment Directive UWWTD, adopted in 2024. This report follows (and essentially supersedes) a previous report (RSA/EFP001_001).

Information provided by the Commission under a Freedom of Information (FoI) request provides greater transparency about the approach taken and how the 66% figure was calculated. However, major concerns about the quality and bias of some of the underlying data have been identified, which suggests that the calculated toxic load for pharmaceuticals has been greatly overestimated.

Biased data selection

The Commission's approach is highly selective in terms of the data sources used. Specifically, large reliance is placed on ecotoxicity data contained within a single paper by Pistocchi *et al.* (2022) when clearly relevant higher quality PNEC data are publicly available from other more reliable data sources.

In addition, for 103 pharmaceuticals only, additional market data have been used by the Commission to calculate concentrations in wastewater, thereby increasing the apparent overall contribution from pharmaceuticals. The use of market data in this way (i.e. for pharmaceuticals only but not for other substances) introduces significant bias in inflating toxic loads for pharmaceuticals in comparison to other substances.

Disproportionate data availability

It is striking that 40% of the micropollutants in the Commission's data have "-1" (undefined) assigned to wastewater concentrations, however only 10% of these (4% of the total) are for pharmaceuticals. Since pharmaceuticals comprise 27% of all micropollutants in the Commission's analysis there is a disproportionate amount of data on pharmaceutical wastewater concentrations which are not available for other industry sectors. This skewed availability of data is exacerbated by, and mostly caused by, the use of market data for pharmaceuticals.

Disproportionately high toxic load from using market data

When refined PNEC data are taken into account, 36% of the total toxic load from pharmaceuticals relies on market data. This is significant since market data does not take into account any human metabolism or degradation and therefore represents a worst case based on the total residue. There is nothing necessarily wrong with this approach per se, since the Commission definition of micropollutant includes metabolites and transformation products. However, in comparison to other substances, wastewater concentrations calculated from market data are likely to

represent a disproportionately high toxic load compared to those calculated from measured concentrations.

When these factors are considered alongside the already disproportionately higher availability of wastewater concentrations for pharmaceuticals compared to other substances, the potential for bias in inflating toxic loads for pharmaceuticals is potentially very significant.

Use of poor quality PNECs

Major concerns about the quality of some of the underlying data for deriving PNECs have been identified, in particular the use of *in-silico* data when reliable empirical ecotoxicity data are readily available. PNECs derived using *in-silico* data are often several orders of magnitude lower than those derived from reliable empirical data, therefore the calculated toxic load for several pharmaceuticals has been greatly overestimated.

- Using the Commission data 'as-is', the active pharmaceutical ingredient telmisartan contributes 41% of the total toxic load of all substances, however this is simply an artifact of the PNEC being based on predicted (*in-silico*) data. When reliable chronic laboratory ecotoxicity data are used, the contribution of telmisartan reduces to almost zero and the total contribution from all pharmaceuticals reduces from 66% to 42% of the total toxic load.

- Further refinement of the data using reliable PNECs based on laboratory ecotoxicity data brings the total contribution to toxic load from all pharmaceuticals down to 18%.

In general, where reliable empirical ecotoxicity data are available these are always preferred for environmental risk assessment in the EU and are specifically required for pharmaceuticals under EMA Guidelines (EMA, 2024). It would therefore seem appropriate that the same principles and expectations for high quality data should apply in the Commission's calculation of toxic loads, however this is currently not the case.

The toxic load contributions from different sectors could potentially be refined further by using more reliable PNECs for other substances (i.e. not just pharmaceuticals), however this has not been investigated.

Potentially overestimated wastewater concentrations

The comparison of worst-case PECs (assuming 100% excretion and no removal during wastewater treatment) against the wastewater concentrations used by the Commission identified 7 pharmaceuticals where MECs seemed high (more than a factor of 10) compared to worst-case PECs. These findings require cautious interpretation, since they may not be showing a like-for-like comparison and comparable PECs and MECs were available for less than half on the pharmaceuticals on the Commissions list. For a more comprehensive reality-check of

MECs used by the Commission, it is recommended to obtain IQVIA sales (Kg) data for all pharmaceuticals in the Commission's list.

Oversimplistic assignment of industry sectors

The Commission's approach assigns each substance to a single sector, whereas in reality this is over-simplistic. For example, some pharmaceuticals are also naturally occurring substances in wastewater (e.g. estradiol and other hormones excreted naturally by humans), while others are used in multiple sectors (e.g. in veterinary medicines and agricultural settings).

Probably the most important factor in the Commission's analysis is the exclusion of non-household sources (e.g. from rain water runoff), which seems to be a purely political decision, since micropollutants also enter wastewater treatment facilities via rain water run-off. From a scientific perspective this approach is highly problematic for interpreting wastewater concentrations, since the relative proportion of MECs arising from household vs non-household origin is rarely known.

A more rigorous assessment of sector allocation could potentially reduce the apportionment of toxic load to human pharmaceuticals. However, to avoid bias in refining sector allocations, it would be important to consider all substances in the Commission's list. This would require further research and it is not clear what the impact would be on overall toxic load allocations from each sector.

Impact of tertiary level treatment

Similar to the issue of sector allocation, a more rigorous assessment of removal during tertiary treatment could potentially reduce the apportionment of toxic load to some human pharmaceuticals. However, the same is also true for non-pharmaceutical substances, therefore, to avoid bias, it would be important to consider all substances in the Commission's list. This would require further research and it is not clear what the impact would be on overall toxic load allocations from each sector.

2 INTRODUCTION

At the request of EFPIA, RSA has undertaken an analysis of data used by the European Commission (the Commission) to calculate the 66% toxic load which it has attributed to pharmaceuticals as a basis for allocating costs under Extended Producer Responsibility (EPR) Schemes in accordance with the recast EU Urban Wastewater Treatment Directive UWWTD, adopted in 2024.

New information provided by the Commission under a Freedom of Information (FoI) request provides greater transparency about the approach taken and how the 66% figure was calculated. The new information is hereafter referred to as the "FoI data".

The FoI data was converted from a pdf into an Excel file (Appendix 1) in order to reproduce the Commission's calculations and to assess the impact of using alternative data and assumptions. In particular, the following areas were explored;

i) The impact of using more reliable PNEC values

ii) The representativeness of wastewater concentrations

iii) Industry Sector allocation to toxic load

iv) Impact of Treatment level assumed

v) Impact of bias in data selection and refinement

Key to the Commission's approach is the concept of "toxic load". For any given substance, the toxic load is calculated as the ratio between the "concentration in wastewater" and the predicted no effect concentration (PNEC). The toxic load for each substance is given in the last column "Toxic load PNEC (calculated, adimensional)" in Appendix 1.

The toxic load contribution of all substances in the FoI data is calculated as 8830. This figure is taken to represent 100% of the toxic load to a typical urban WWTP. Using the Commission's approach, the relative contribution from an individual substance or group of substances may then be determined as a percentage of this total toxic load.

The toxic load from all substances identified as "Pharma" is 5840 which represents 66% of the total toxic load (5840/8830).

With the FoI data converted into an Excel file it is possible to investigate different scenarios by using alternative data. For example, the FoI data shows that the active pharmaceutical ingredient telmisartan alone contributes a toxic load of 3623, representing 41% of the total toxic load of all micropollutants. This is an erroneous value, caused by an inappropriate PNEC (discussed in this report) but highlights an important point; if the PNEC for telmisartan is corrected, its toxic load reduces to almost zero. However, this also reduces the total toxic load of all substances by a corresponding amount, which in turn changes the relative contributions of all the other substances, since the total will always be 100% using the Commission's approach.

This “normalisation” to 100% is important to bear in mind when interpreting the Commission’s analysis and the results of the analyses included in this report, since a) this approach is extremely susceptible to bias if data selection and refinement is only undertaken in selected areas of interest, and b) successive refinement of underlying data will inevitably highlight different substances contributing to the majority of the toxic load.

Note; This report follows (and essentially supersedes) a previous report (RSA/EFP001_001) which was written before the FoI data were provided.

3 METHODS

The FoI data were converted from a pdf into an Excel file (Appendix 1) in order to reproduce the Commission’s calculations and to explore the following areas:

3.1 Impact of using more reliable PNEC values

A number of reliable PNECs were identified from publicly available data, including published data Gunnarsson *et al.* (2019) and environmental quality standards (EQS) established under the EU Water Framework Directive.

Specifically, the following data sources were used;

1) Proposed EQS values under Annex 1 of Directive 2008/105/EC
2) PNECs from Gunnarsson *et al.* (2019) for which chronic ecotoxicity data were available for three trophic levels (using an Assessment Factor of 10). This is consistent with the highest quality of data expected for human medicinal products required by the European Medicines Agency (EMA, 2024).
3) A PNEC of 23600 ng/L for dipyridamole based on empirical data from the Norman database, accessed 27 May 2025. [Note, the Commission’s value of 5.3 ng/L was also previously from the Norman database according to Pistocchi *et al.* (2022), however this value appears to be no longer available in Norman].

The impact of using the different data sources was assessed using the Excel version of the FoI data.

[Note, the 27 PNECs used in the previous report (RSA/EFP001_001) were included in the above data and these were used for comparison purposes and as a point of reference to understand the impact of using the new FoI data].

3.2 Representativeness of wastewater concentrations

Unlike the PNECs, there are no obvious alternative data sources for measured wastewater concentrations (MECs), or predicted environmental concentrations (PECs).

Two approaches were taken in this review; i) a comparison of worst-case PECs from Canata *et al.* (2024) against the wastewater concentrations in the FoI data and ii) a review of the potential impact of bias in using market data to calculate wastewater concentrations.

3.2.1 Comparison against PECs from Cannata *et al.* (2024)

Theoretically, if worst case PECs (based on sales (kg) averaged over a year) are much lower than the wastewater concentrations used by the Commission, it may be reasonable to question whether the latter are representative of household emissions of pharmaceuticals, which is what the EPR allocation is supposed to be based on according to the Commission's approach.

Wastewater concentrations contained in the FoI data were compared against theoretical maximum concentrations reported in Cannata *et al.* (2024). Cannata *et al.* provide estimated consumption data (based on IQVIA MIDAS® kilogram sales data) and corresponding PEC data for approximately 1400 substances, mostly pharmaceuticals, of which 155 have comparable data included on the FoI list of micropollutants. The Cannata *et al.* PECs assume 100% excretion and zero removal during wastewater treatment, and therefore provide a worst-case estimate of exposure.

The surface water PECs provided in Cannata *et al.* (2024) were multiplied by a factor of 10 to provide worst-case predicted wastewater influent concentrations. Excel Index and Match functions were then used to compare values against wastewater concentrations in the FoI data.

3.2.2 Impact of bias in using market data

The potential for introducing bias in selecting effluent concentrations was investigated by comparing toxic loads with and without using market data for pharmaceuticals. In the FoI data the Commission used a secondary data source of market data for 103 pharmaceuticals, of which 55 had available PNECs and calculated toxic loads. The total toxic load for these 55 substances was calculated and discussed in relation to potential bias introduced.

3.3 Industry Sector allocation to toxic load

Examples were identified where assumed sector allocation is questionable, focusing on pharma-assigned substances which have a high toxic load, but which are in reality used in multiple sectors or come from natural sources. The potential impact on pharma toxic load, if sector allocation for these substances were assigned more appropriately.

3.4 Impact of treatment level assumed

Examples were identified where treatment removal is potentially significant, focusing on pharma substances which have a high toxic load, but which in reality are expected to be removed from wastewater. The potential impact on pharma toxic load is considered, if removal is taken into account.

3.5 Impact of bias (more generally) in data selection and refinement

This issue is discussed in general terms, (i.e. not just in relation to wastewater concentrations).

4 RESULTS AND DISCUSSION

4.1 Impact of using more reliable PNEC values

The impact of using the different data sources summarized in Section 3.1 was assessed using the Excel version of the FoI data. The results are summarized in Table 1 and the following sub-sections.

Table 1 Summary of Selected Toxic Load Contributions using different PNEC Data Sources

Toxic Load (as % of total)	Total from all 1294 substances considered for EPR	Total from Pharma substances	Telmisartan alone	Dipyridamole alone	Permethrin alone
Scenario 1 Commission data as-is	8830	5840	3623	774	1450
	(100%)	(66%)	(41%)	(9%)	(16%)
Scenario 2 Replacing with reliable PNEC for Telmisartan	5229	2217	0.041	774	1450
	(100%)	(42%)	(0.0008%)	(15%)	(28%)
Scenario 3 Replacing with 27 reliable PNECs from RSA/EFP001_001	3573	935	0.041	0.17	1074
	(100%)	(26%)	(0.0011%)	(0.0049%)	(30%)
Scenario 4 Replacing with reliable PNECs from Gunnarsson *et al.* (2019)	4261	1249	0.041	774	1450
	(100%)	(29%)	(0.0010%)	(18%)	(34%)
Scenario 5 Replacing with reliable EQS	8260	5756	3623	774	1074
	(100%)	(70%)	(44%)	(9%)	(13%)
Scenario 6 Replacing with reliable PNECs from Gunnarsson *et al.* (2019) & EQS	3833	1330	0.041	774	1074
	(100%)	(35%)	(0.0011%)	(20%)	(28%)
Scenario 7 As Scenario 6 plus Replacing with dipyridamole PNEC from Norman database	3060	556	0.041	0.17	1074
	(100%)	(18%)	(0.0013%)	(0.0057%)	(35%)

Scenario 1 – Analysis of FoI data as provided

This scenario clearly shows how the 66% contribution from pharmaceuticals has been derived by the Commission and which substances have been identified as 'Pharma'. The telmisartan contribution is clearly erroneous (based on *in-silico* prediction of acute toxicity), comprising 41% of the total toxic load in the Commission's analysis. The pharmaceutical dipyridamole and permethrin comprise 16% and 9%, respectively, and provide reference points for comparison in later scenarios.

Note that the total toxic load from all substances is 8830 and this is taken to represent 100% of the toxic load from micropollutants considered for potential EPR inclusion in the Commission's analysis.

Scenario 2 – Substituting the Telmisartan PNEC with empirical data

This removes the erroneous toxic load from telmisartan, however this also decreases the total toxic load of all substances to 5229 (which becomes the 'new' 100%). Consequently the total contribution from pharmaceutical becomes 42% (instead of 66%). Note that the contributions from dipyridamole and permethrin increase to 15% and 28%, respectively.

Scenario 3 – Replacing the 27 PNECs (as previously done in report RSA/EFP001_001)

The total toxic load of all substances in this scenario is 3573 which is less than half the total load calculated in the Commission's analysis (Scenario 1). The total pharmaceutical contribution in this scenario decreases to 26%. This is somewhat higher than the 6.8% previously determined for the same scenario in the previous report (RSA/EFP001_001). Both dipyridamole and telmisartan effectively drop to near zero since these were two of the 27 PNECs with much lower toxicity than assumed by the Commission. The contribution of permethrin increases to 30% under this scenario.

Scenario 4 - Using the 42 PNECs from Gunnarsson *et al.* (2019)

This scenario uses high quality replacement PNECs from Gunnarsson *et al.* for 42 of the pharmaceutical substances contained in the Commission's list. The total contribution is 29%. Dipyridamole was not included in the Gunnarsson paper so this becomes the major pharmaceutical contribution in this scenario, comprising 18% of the total toxic load (and over half of the total toxic load from pharmaceuticals).

Scenario 5 - Using 56 EQS values currently proposed under the EU Water Framework Directive.

This scenario uses all of the proposed EQS values in Annex 1 of Directive 2008/105/EC. Some, but not all values, were the same as those used by the Commission. The list contains a few pharmaceuticals, but not many (and not telmisartan or dipyridamole, for example). The total toxic load in this scenario is higher than in the Commission's analysis and the total pharmaceutical contribution is 70%, with telmisartan contributing 44% alone.

Scenario 6 – Using both Gunnarsson PNECs and WFD EQSs (with duplicates removed).

This scenario uses all the PNECs from Gunnarsson *et al.* (2019) and all the EQS values proposed EQS values in Annex 1 of Directive 2008/105/EC. This combined list includes all of the original 27 substances considered in RSA/EFP001_001, except for dipyridamole. The list also includes 17 substances for which no PNEC is defined in the FoI data. The total toxic load under this scenario is 3043 and the

pharmaceutical contribution is 35%. Dipyridamole and permethrin contribute 20% and 28%, respectively.

Scenario 7 - Using both Gunnarsson PNECs and WFD EQS plus the additional PNEC for dipyridamole (with duplicates removed).

This scenario uses all the PNECs from Gunnarsson *et al.* (2019), all the EQS values in Annex 1 of Directive 2008/105/EC and a PNEC for dipyridamole based on empirical data from the Norman database (as a replacement for the in-silico value used by the Commission). The inclusion of the replacement PNEC for dipyridamole brings the overall pharmaceutical contribution down to 18%. Permethrin alone contributes 35% of the toxic load under this scenario.

The impact of using more accurate PNECs is obvious, particularly at an individual substance level. Using the Commission data 'as-is', the active pharmaceutical ingredient telmisartan contributes 41% of the total toxic load of all substances, however this is simply an artifact of the PNEC being based on predicted (*in-silico*) data. When the PNEC for telmisartan alone is replaced by a PNEC based on reliable chronic laboratory ecotoxicity data, the contribution reduces to 0.0008% and the total contribution from all pharmaceuticals reduces from 66% to 42% of the total toxic load.

In general, where reliable empirical ecotoxicity data are available these are always preferred for environmental risk assessment in the EU and are specifically required for pharmaceuticals under EMA Guidelines (EMA, 2024). It would therefore seem appropriate that the same principles and expectations for high quality data should apply in the Commission's calculation of toxic loads, however this is currently not the case.

The toxic load contributions from different sectors could almost certainly be refined further by using more reliable PNECs for other substances (i.e. not just pharmaceuticals), however this has not been investigated.

4.2 Representativeness of wastewater concentrations

4.2.1 Comparison against PECs from Cannata *et al.* (2024)

Unlike the PNECs, there are no obvious alternative data sources for measured wastewater concentrations (MECs), or predicted environmental concentrations (PECs). Nevertheless, the wastewater concentrations are equally as important as the PNECs for calculating toxic load, and therefore ideally warrant an equal emphasis on quality and representativeness.

Standards do exist against which MEC/PEC data can be reviewed for relevance and reliability (e.g. using CREED criteria), however this would require extensive effort to review the original data sources. In theory the effluent concentrations based on Cannata *et al.* surface water PECs, (applying a dilution factor of 10), should approximate a reasonable worst case, since no human metabolism or degradation is taken into account. Therefore, those substances for which the FoI data show higher

wastewater concentrations than those calculated from Cannata *et al.* are shown in Table 2.

Table 2 ranks substances from highest to lowest ratio of FoI/Cannata wastewater concentration and it is clear that some substances have a much higher concentration in the FoI data compared to those predicted by Cannata *et al.* The top 7 substances have wastewater concentrations 10 times higher than predicted based on based on sales (kg) averaged over a year data, including the pharmaceuticals pentobarbital, secobarbital, thiabendazole, amphetamine and lorazepam. Of these, pentobarbital, secobarbital and thiabendazole are primarily veterinary drugs and amphetamine is known for drug misuse which may account for the high proportion of non-prescribed volume used. Why the lorazepam MEC should be >10 times the worst-case PEC is unclear.

Table 2 Comparison of wastewater concentrations against theoretical maximum influent concentrations of pharmaceuticals from Cannata *et al.*, 2024

CAS number	Substance name	Sector Assigned	Concentration in wastewater from FoI data (ng/L)	Toxic load (calculated, adimensional)	Cannata PEC *10 (ng/L)	Concentration in Wastewater / Cannata PEC
83-67-0	Theobromine	Food product	199	0.0020	0.00015	1371694.840
76-74-4	Pentobarbital	Pharma	471	0.0095	0.00129	365764.444
76-73-3	Secobarbital	Pharma	4702	1.1091	0.31462	14945.189
148-79-8	Thiabendazol	Pharma	37	0.0112	0.00428	8649.493
50-36-2	Cocaine	Other	234	0.0951	0.70076	333.926
300-62-9	Amphetamine	Pharma	301	0.0121	8.04567	37.411
846-49-1	Lorazepam	Pharma	842	8.7656	60.29	13.966
58-73-1	Diphenhydramine	Pharma	1447	1.4613	216.47	6.685
69-72-7	Salycilic acid	Pharma	15500	0.8611	2591.11	5.982
23031-25-6	terbutaline	Pharma	88	0.0050	15.90	5.534
3380-34-5	Triclosan	PCP	720	36.0000	139.76	5.152
6740-88-1	Ketamine	Pharma	75	0.0131	20.76	3.613
58-32-2	dipyridamole	Pharma	4100	773.5849	1567.80	2.615
846-50-4	Temazepam	Pharma	440	6.1972	171.63	2.564
58-55-9	Theophyllin	PCP	5400	0.3649	3039.71	1.776
54739-18-3	Fluvoxamine	Pharma	304	0.1220	180.72	1.682
24280-93-1	Mycophenolic acid	Pharma	900	0.3180	538.88	1.670
3930-20-9	Sotalol	Pharma	1300	0.1994	894.79	1.453
94-24-6	Tetracain	Pharma	15	0.0161	10.67	1.406
52645-53-1	Permethrin	PCP	290	1450.0000	204.02	1.421
5633-20-5	Oxybutynin	Pharma	45	0.0512	31.77	1.417
80-08-0	Dapsone92	Pharma	21	0.0150	16.25	1.293
768-94-5	Amantadine	Pharma	267	0.0107	216.44	1.234

224785-90-4	Vardenafil	Pharma	3	0.0414	2.86	1.049
604-75-1	Oxazepam	Pharma	670	1.8103	556.62	1.204
58-93-5	Hydrochlorothiazid	Pharma	4365	0.5208	3648.08	1.197
4205-90-7	Clonidine	Pharma	1	0.0003	0.71	1.417
139481-59-7	Candersartan	Pharma	1266	408.3700	1156.51	1.095
114798-26-4	Losartan	Pharma	7001	0.0898	6515.72	1.074

The comparison of worst-case PECs against the wastewater concentrations used by the Commission requires cautious interpretation, since they may not be showing a like-for-like comparison. Dilution factors corresponding to MECs may be more or less than 10, depending on the sampling location, for example.

However, if worst-case PECs (based on sales (kg) averaged over a year) are much lower than the FoI data, it may be reasonable to question whether the FoI effluent concentration data are representative of household emissions of pharmaceuticals, which is what the EPR allocation should be based on.

Note that comparable data were only available for 155 out of 348 pharmaceuticals on the Commission's list, therefore this comparison will miss potential discrepancies for other compounds. The purpose is more to highlight the potential for such discrepancies to occur. For a more comprehensive reality-check of MECs used by the Commission, it is recommended to obtain IQVIA sales (Kg) data for all pharmaceuticals in the Commission's list.

4.2.2 Impact of bias in using market data

It is striking that 40% of the micropollutants in the FoI data have "-1" (undefined) assigned to wastewater concentrations, however only 10% of these (4% of the total) are for pharmaceuticals. Since pharmaceuticals comprise 27% of all micropollutants in the Commission's analysis there appears to be a disproportionate amount of data on pharmaceutical wastewater concentrations which are not available for other industry sectors. This skewed availability of data is exacerbated by, and mostly caused by, the use of market data for pharmaceuticals.

The impact of using market data to calculate toxic loads is summarized in Table 3. The columns 'All substances' and 'Pharma substances only' are the same as the first two columns in Table 1 for scenarios 1 and 7, respectively. The final column shows the contribution of pharmaceuticals based on the market data used by the Commission.

Table 3 shows that in the Commission's analysis (Scenario 1), approximately 6% of the total toxic load from all substances is based on market data for pharmaceuticals. This represents 10% of the total pharmaceutical toxic load calculated by the Commission.

Table 3 also shows the equivalent results for Scenario 7 (using all available and reliable replacement PNECs). This scenario shows a similar proportion (7%) of the total toxic load from all substances coming from market data for pharmaceuticals. However, this now represents 36% of the total pharmaceutical toxic load calculated

in this scenario. In other words, a higher proportion of the pharmaceutical toxic load relies on market data when the high-quality replacement PNEC data are used.

Table 3 Impact on toxic load of Pharmaceuticals from using market data

		All substances	Pharma substances only	Pharma substances based on market data only
Scenario 1 Commission data as-is	Total toxic load	8853	5840	566.00
	% of total of all substances	100%	66%	6%
	% of total of pharma substances		100%	10%
Scenario 7 + Replacing dipyridamole PNEC	Total toxic load	3060	556	200.06
	% of total of all substances	100%	18%	7%
	% of total of pharma substances		100%	36%

This is potentially significant since the use of market data does not take into account any human metabolism or degradation and therefore represents a worst case based on the total residue, which is consistent with the approach used in EMA environmental risk assessment guideline. The point is that wastewater concentrations based on measured concentrations do not usually quantify levels of metabolites or transformation products, unless these are specifically analysed for. Therefore, in comparison to other substances, wastewater concentrations calculated from market data are likely to represent a disproportionately high toxic load compared to those calculated from measured concentrations.

When these factors are considered alongside the already disproportionately higher availability of wastewater concentrations for pharmaceuticals compared to other substances, the potential for bias in inflating toxic loads for pharmaceuticals is potentially very significant.

For those substances where the Commission used market data, wastewater concentrations in the FoI data were broadly similar or less than those calculated from Canata *et al.* (2024), therefore there is no indication of bias in terms of the values used per se. The main potential for bias lies in the very fact that these data were used at all, whereas equivalent data for other industry sectors have not been used.

4.3 Industry Sector allocation to toxic load

A more rigorous assessment of sector allocation could potentially reduce the apportionment of toxic load to human pharmaceuticals, for example through consideration of substances used in multiple industry sectors, substances which are also naturally occurring (such as estradiol), and substances derived from household vs non-household settings.

The latter is relevant, since measured wastewater concentrations do not distinguish between household versus non-household sources, and hence may overestimate the contribution from households if the relative contribution from non-household sources is not taken into account. However, the same is also true for non-

pharmaceutical substances and the same approach for other sectors could potentially increase the relative contribution from pharmaceuticals. Therefore, to avoid bias, it would be important to consider all substances in the Commission's list. This would require further research beyond the scope of this report, and it is not clear what the impact would be on overall toxic load allocations from each sector.

Probably the most important factor in the Commission's approach is the exclusion of non-household sources (e.g. from rain water runoff), which seems to be a purely political decision. From a scientific perspective this approach is also highly problematic for interpreting wastewater concentrations, since the relative proportion of MECs arising from household vs non-household origin is rarely known.

4.4 Impact of treatment level assumed

Similar to the issue of sector allocation, a more rigorous assessment of removal during tertiary treatment could potentially reduce the apportionment of toxic load to human pharmaceuticals. However, the same is also true for non-pharmaceutical substances, therefore, to avoid bias, it would be important to consider all substances in the Commission's list. This would require further research beyond the scope of this report, and it is not clear what the impact would be on overall toxic load allocations from each sector.

On an individual substance level, consideration of ready biodegradability is taken into account separately within the proposed EPR approach, so companies marketing substances that are readily biodegradable may be exempt from payment to EPR schemes for those substances. However, for the purpose of defining the overall 66% contribution from pharmaceuticals to toxic load in the Commission's approach, the biodegradability of substances does not appear to be taken into account. It is possible that it is implicit in the wastewater concentrations listed but this is not clear from the information provided.

4.5 Impact of bias (more generally) in data selection and refinement

The potential bias introduced from using market data for pharmaceuticals has already been discussed in Section 4.2.2.

More generally, the Commission's approach to assigning toxic load to pharmaceuticals (or any industry sector) is highly susceptible to bias, and potentially very sensitive to any changes made to underlying data, for PNECs as well as MECs.

In the scenarios evaluated above, if only EQS data are used in isolation (which includes very few pharmaceuticals) the toxic load contribution from pharma is 70%. If only Gunnarsson *et al.* data are used in isolation the toxic load contribution from pharma is 29%. This simply highlights how using data selectively can give very different results. If both EQS and Gunnarsson data sources are used – arguably a more balanced approach - the contribution from pharma is 35%. Adding the high quality PNEC for dipyridamole reduces the contribution from pharma to 18%.

Whilst these high quality PNEC refinements are completely justified from a data quality perspective, they only reflect a small proportion of the substances on the Commission's list, and are biased towards pharmaceuticals (Gunnarsson *et al.*) and substances of known concern in the EU (EQSs). Robust PNECs for other

substances will almost certainly be available in other industry sectors and it is highly likely that the relative contributions from different sectors would change again if these PNECs are taken into account.

Note that focusing only on the top-contributing substances will inevitably introduce bias into the analysis to some extent, and lead to a different result than might be obtained if all substances were reviewed using the same data criteria. Minimising such bias would require evaluating all substances against the same criteria to ensure comparison of like-with-like.

The above paragraphs highlight the need (ideally) for a non-biased approach that both a) uses the most appropriate and representative information available for calculating toxic load contributions of substances and b) uses a consistently rigorous approach for assessing data quality for all substances, not just pharmaceuticals or those that appear to contribute highly to toxic load.

5 CONCLUSIONS

At the request of EFPIA, RSA has undertaken an analysis of data used by the European Commission (the Commission) to calculate the 66% toxic load which it has attributed to pharmaceuticals as a basis for allocating costs under Extended Producer Responsibility (EPR) Schemes in accordance with the recast EU Urban Wastewater Treatment Directive UWWTD, adopted in 2024. This report follows (and essentially supersedes) a previous report (RSA/EFP001_001).

Information provided by the Commission under a Freedom of Information (FoI) request provides greater transparency about the approach taken and how the 66% figure was calculated. However, major concerns about the quality and bias of some of the underlying data have been identified, which suggests that the calculated toxic load for pharmaceuticals has been greatly overestimated.

Biased data selection

The Commission's approach is highly selective in terms of the data sources used. Specifically, large reliance is placed on ecotoxicity data contained within a single paper by Pistocchi *et al.* (2022) when clearly relevant higher quality PNEC data are publicly available from other more reliable data sources.

In addition, for 103 pharmaceuticals only, additional market data have been used by the Commission to calculate concentrations in wastewater, thereby increasing the apparent overall contribution from pharmaceuticals. The use of market data in this way (i.e. for pharmaceuticals only but not for other substances) introduces significant bias in inflating toxic loads for pharmaceuticals in comparison to other substances.

Disproportionate data availability

It is striking that 40% of the micropollutants in the Commission's data have "-1" (undefined) assigned to wastewater concentrations, however only 10% of these (4%

of the total) are for pharmaceuticals. Since pharmaceuticals comprise 27% of all micropollutants in the Commission's analysis there is a disproportionate amount of data on pharmaceutical wastewater concentrations which are not available for other industry sectors. This skewed availability of data is exacerbated by, and mostly caused by, the use of market data for pharmaceuticals.

Disproportionately high toxic load from using market data

When refined PNEC data are taken into account, 36% of the total toxic load from pharmaceuticals relies on market data. This is significant since market data does not take into account any human metabolism or degradation and therefore represents a worst case based on the total residue. There is nothing necessarily wrong with this approach per se, since the Commission definition of micropollutant includes metabolites and transformation products. However, in comparison to other substances, wastewater concentrations calculated from market data are likely to represent a disproportionately high toxic load compared to those calculated from measured concentrations.

When these factors are considered alongside the already disproportionately higher availability of wastewater concentrations for pharmaceuticals compared to other substances, the potential for bias in inflating toxic loads for pharmaceuticals is potentially very significant.

Use of Poor quality PNECs

Major concerns about the quality of some of the underlying data for deriving PNECs have been identified, in particular the use of *in-silico* data when reliable empirical ecotoxicity data are readily available. PNECs derived using *in-silico* data are often several orders of magnitude lower than those derived from reliable empirical data, therefore the calculated toxic load for several pharmaceuticals has been greatly overestimated.

- Using the Commission data 'as-is', the active pharmaceutical ingredient telmisartan contributes 41% of the total toxic load of all substances, however this is simply an artifact of the PNEC being based on predicted (*in-silico*) data. When reliable chronic laboratory ecotoxicity data are used, the contribution of telmisartan reduces to almost zero and the total contribution from all pharmaceuticals reduces from 66% to 42% of the total toxic load.

- Further refinement of the data using reliable PNECs based on laboratory ecotoxicity data brings the total contribution to toxic load from all pharmaceuticals down to 18%.

In general, where reliable empirical ecotoxicity data are available these are always preferred for environmental risk assessment in the EU and are specifically required for pharmaceuticals under EMA Guidelines (EMA, 2024). It would therefore seem appropriate that the same principles and expectations for high quality data should

apply in the Commission's calculation of toxic loads, however this is currently not the case.

The toxic load contributions from different sectors could potentially be refined further by using more reliable PNECs for other substances (i.e. not just pharmaceuticals), however this has not been investigated.

Potentially overestimated wastewater concentrations

The comparison of worst-case PECs (assuming 100% excretion and no removal during wastewater treatment) against the wastewater concentrations used by the Commission identified 7 pharmaceuticals where MECs seemed high (more than a factor of 10) compared to worst-case PECs. These findings require cautious interpretation, since they may not be showing a like-for-like comparison and comparable PECs and MECs were available for less than half on the pharmaceuticals on the Commissions list. For a more comprehensive reality-check of MECs used by the Commission, it is recommended to obtain IQVIA sales (Kg) data for all pharmaceuticals in the Commission's list.

Oversimplistic assignment of industry sectors

The Commission's approach assigns each substance to a single sector, whereas in reality this is over-simplistic. For example, some pharmaceuticals are also naturally occurring substances in wastewater (e.g. estradiol and other hormones excreted naturally by humans), while others are used in multiple sectors (e.g. in veterinary medicines and agricultural settings).

Probably the most important factor in the Commission's analysis is the exclusion of non-household sources (e.g. from rain water runoff), which seems to be a purely political decision, since micropollutants also enter wastewater treatment facilities via rain water run-off. From a scientific perspective this approach is highly problematic for interpreting wastewater concentrations, since the relative proportion of MECs arising from household vs non-household origin is rarely known.

A more rigorous assessment of sector allocation could potentially reduce the apportionment of toxic load to human pharmaceuticals. However, to avoid bias in refining sector allocations, it would be important to consider all substances in the Commission's list. This would require further research and it is not clear what the impact would be on overall toxic load allocations from each sector.

Impact of tertiary level treatment

Similar to the issue of sector allocation, a more rigorous assessment of removal during tertiary treatment could potentially reduce the apportionment of toxic load to some human pharmaceuticals. However, the same is also true for non-pharmaceutical substances, therefore, to avoid bias, it would be important to consider all substances in the Commission's list. This would require further research

and it is not clear what the impact would be on overall toxic load allocations from each sector.

6 REFERENCES

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7 APPENDICES

Appendix 1 Data obtained from the Commission via FoI request (FoI data "as-is", converted into Excel

Appendix 2 FoI PNECs compared to Alternative High Quality PNECs

Substance	CAS no.	FoI PNEC used in Commission's analysis (ng/L) (-1's indicate no data used)	Alternative PNEC (ng/L)	Reference
Chlorfenvinphos	470-90-6	100	100	Annex 1 of EQS Directive 2008/105/EC
Simazine	122-34-9	1000	1000	Annex 1 of EQS Directive 2008/105/EC
Anthracene	120-12-7	100	100	Annex 1 of EQS Directive 2008/105/EC
Atrazine	1912-24-9	600	600	Annex 1 of EQS Directive 2008/105/EC
Benzene	71-43-2	10000	10000	Annex 1 of EQS Directive 2008/105/EC
Chlorpyrifos	2921-88-2	30	0.46	Annex 1 of EQS Directive 2008/105/EC
Aldrin	309-00-2	10	10	Annex 1 of EQS Directive 2008/105/EC
Dieldrin	60-57-1	-1	10	Annex 1 of EQS Directive 2008/105/EC
Endrin	72-20-8	-1	10	Annex 1 of EQS Directive 2008/105/EC
Isodrine	465-73-6	10	10	Annex 1 of EQS Directive 2008/105/EC
p,p-DDT	50-29-3	10	10	Annex 1 of EQS Directive 2008/105/EC
1,2-Dichloroethan1	107-06-2	10000	10000	Annex 1 of EQS Directive 2008/105/EC
Di(2-ethylhexyl)phthalate (DEHP)	117-81-7	1300	1300	Annex 1 of EQS Directive 2008/105/EC
Diuron	330-54-1	70	49	Annex 1 of EQS Directive 2008/105/EC
Endosulfan	115-29-7	-1	5	Annex 1 of EQS Directive 2008/105/EC
Fluoranthene	206-44-0	6.3	0.762	Annex 1 of EQS Directive 2008/105/EC
hexachlorobenzene	118-74-1	50	500	Annex 1 of EQS Directive 2008/105/EC
Hexachlorobutadiene	87-68-3	600	0.9	Annex 1 of EQS Directive 2008/105/EC
Hexachlorocyclohexane	608-73-1	20	20	Annex 1 of EQS Directive 2008/105/EC
hexabromocyclododecane	25637-99-4	-1	0.46	Annex 1 of EQS Directive 2008/105/EC
Isoproturon	34123-59-6	300	300	Annex 1 of EQS Directive 2008/105/EC
Naphthalene	91-20-3	2000	2000	Annex 1 of EQS Directive 2008/105/EC
Nonylphenol	84852-15-3	-1	37	Annex 1 of EQS Directive 2008/105/EC
(4-(1,1',3,3'-tetramethylbutyl)-phenol)	140-66-9	100	100	Annex 1 of EQS Directive 2008/105/EC
pentachlorobenzene	608-93-5	7	7	Annex 1 of EQS Directive 2008/105/EC

Substance	CAS no.	FoI PNEC used in Commission's analysis (ng/L) (-1's indicate no data used)	Alternative PNEC (ng/L)	Reference
Pentachlorophenol	87-86-5	400	400	Annex 1 of EQS Directive 2008/105/EC
Benzo[a]pyrene	50-32-8	0.17	270	Annex 1 of EQS Directive 2008/105/EC
benzo(b)fluoranthene	205-99-2	17	17	Annex 1 of EQS Directive 2008/105/EC
Benzo(k)fluoranthene	207-08-9	17	17	Annex 1 of EQS Directive 2008/105/EC
Benzo[ghi]perylene	191-24-2	8.2	8.2	Annex 1 of EQS Directive 2008/105/EC
Chrysene	218-01-9	2.9	70	Annex 1 of EQS Directive 2008/105/EC
benzo(a)antracene	56-55-3	12	100	Annex 1 of EQS Directive 2008/105/EC
Dibenzo[a,h]anthracene	53-70-3	1.4	14	Annex 1 of EQS Directive 2008/105/EC
Tetrachloroethylene	127-18-4	10000	10000	Annex 1 of EQS Directive 2008/105/EC
perfluorooctane sulfonate (PFOS)	1763-23-1	0.65	4400	Annex 1 of EQS Directive 2008/105/EC
Quinoxyfen	124495-18-7	150	150	Annex 1 of EQS Directive 2008/105/EC
bifenox free acid	53774-07-5	2220	12	Annex 1 of EQS Directive 2008/105/EC
Heptachlor	76-44-8	0.0002	0.00017	Annex 1 of EQS Directive 2008/105/EC
heptachlor epoxide	1024-57-3	0.0002	0.00017	Annex 1 of EQS Directive 2008/105/EC
17b-Estradiol	50-28-2	0.1	0.18	Annex 1 of EQS Directive 2008/105/EC
Azithromycin	83905-01-5	19	19	Annex 1 of EQS Directive 2008/105/EC
carbamazepine	298-46-4	50	2500	Annex 1 of EQS Directive 2008/105/EC
Clarithromycin	81103-11-9	-1	130	Annex 1 of EQS Directive 2008/105/EC
Clothianidin	210880-92-5	2230	10	Annex 1 of EQS Directive 2008/105/EC
Diclofenac	15307-86-5	50	40	Annex 1 of EQS Directive 2008/105/EC
Erythromycin	114-07-8	200	500	Annex 1 of EQS Directive 2008/105/EC
Estrone	53-16-7	3.6	0.36	Annex 1 of EQS Directive 2008/105/EC
Glyphosate	1071-83-6	28000	100	Annex 1 of EQS Directive 2008/105/EC
Ibuprofen	15687-27-1	1000	220	Annex 1 of EQS Directive 2008/105/EC
Permethrin acid	55701-05-8	-1	0.27	Annex 1 of EQS Directive 2008/105/EC
Permethrin	52645-53-1	0.2	0.27	Annex 1 of EQS Directive 2008/105/EC

Substance	CAS no.	FoI PNEC used in Commission's analysis (ng/L) (-1's indicate no data used)	Alternative PNEC (ng/L)	Reference
Thiacloprid	111988-49-9	10	10	Annex 1 of EQS Directive 2008/105/EC
Thiamethoxam	153719-23-4	2960	40	Annex 1 of EQS Directive 2008/105/EC
Tetrachloroethylene	127-18-4	10000	10000	Annex 1 of EQS Directive 2008/105/EC
trichlorobenzenes	12002-48-1	-1	400	Annex 1 of EQS Directive 2008/105/EC
Acetamiprid	135410-20-7	-1	37	Annex 1 of EQS Directive 2008/105/EC
ABIRATERONE	154229-19-3	-1	1.3	Gunnarsson *et al.* (2019)
AMIODARONE	1951-25-3	1.1	1200	Gunnarsson *et al.* (2019)
ANASTROZOLE	120511-73-1	620	1000	Gunnarsson *et al.* (2019)
ATENOLOL	29122-68-7	150000	148000	Gunnarsson *et al.* (2019)
ATORVASTATIN	134523-00-5	10	14000	Gunnarsson *et al.* (2019)
AZELASTINE	58581-89-8	470	11000	Gunnarsson *et al.* (2019)
BETAMETHASONE	5593-20-4	2890	5200	Gunnarsson *et al.* (2019)
BEZAFIBRATE	41859-67-0	2300	1000000	Gunnarsson *et al.* (2019)
BICALUTAMIDE	90357-06-5	520	1000	Gunnarsson *et al.* (2019)
BUPROPION	34911-55-2	4400	1110	Gunnarsson *et al.* (2019)
CANDESARTAN	139481-59-7	3.1	100000	Gunnarsson *et al.* (2019)
CELECOXIB	169590-42-5	90	1100	Gunnarsson *et al.* (2019)
CLOPIDOGREL	113665-84-2	-1	31000	Gunnarsson *et al.* (2019)
DESLORATADINE	100643-71-8	340	36000	Gunnarsson *et al.* (2019)
DIAZEPAM	439-14-5	290	27300	Gunnarsson *et al.* (2019)
DULOXETINE	116539-59-4	180	430	Gunnarsson *et al.* (2019)
ETHINYLESTRADIOL	57-63-6	0.035	0.031	Gunnarsson *et al.* (2019)
FINASTERIDE	98319-26-7	570	5000	Gunnarsson *et al.* (2019)
FLUOROURACIL	51-21-8	58500	280	Gunnarsson *et al.* (2019)
FLUOXETINE	54910-89-3	100	320	Gunnarsson *et al.* (2019)
FULVESTRANT	129453-61-8	-1	0.57	Gunnarsson *et al.* (2019)
HYDROCHLOROTHIAZIDE	58-93-5	8380	1000000	Gunnarsson *et al.* (2019)
IRBESARTAN	138402-11-6	704000	704000	Gunnarsson *et al.* (2019)

Substance	CAS no.	FoI PNEC used in Commission's analysis (ng/L) (-1's indicate no data used)	Alternative PNEC (ng/L)	Reference
LEVONORGESTREL	797-63-7	-1	0.01	Gunnarsson *et al.* (2019)
LORATADINE	79794-75-5	-1	5300	Gunnarsson *et al.* (2019)
LOSARTAN	114798-26-4	78000	1000000	Gunnarsson *et al.* (2019)
METFORMIN	657-24-9	156000	100000	Gunnarsson *et al.* (2019)
MIRTAZAPINE	61337-67-5	1000	32000	Gunnarsson *et al.* (2019)
MOMETASONE	83919-23-7	1260	14	Gunnarsson *et al.* (2019)
MONTELUKAST	158966-92-8	2.2	7300	Gunnarsson *et al.* (2019)
NAPROXEN	22204-53-1	-1	15000	Gunnarsson *et al.* (2019)
PREGABALIN	148553-50-8	-1	100000	Gunnarsson *et al.* (2019)
PROPRANOLOL	318-98-9	-1	200	Gunnarsson *et al.* (2019)
ROSUVASTATIN	287714-41-4	270	1800	Gunnarsson *et al.* (2019)
TAMOXIFEN	10540-29-1	4.1	77	Gunnarsson *et al.* (2019)
TELMISARTAN	144701-48-4	0.55	49000	Gunnarsson *et al.* (2019)
VALSARTAN	137862-53-4	560000	560000	Gunnarsson *et al.* (2019)
DIPYRIDAMOLE	58-32-2	5.3	23600	Norman Database (Accessed 27 May 2025)

Appendix 3 Calculation of toxic loads using both Gunnarsson PNECs and WFD EQS plus the additional PNEC for dipyridamole (with duplicates removed)

CAS Number	Substance	Assigned Sector	Toxic load % contribution	Toxic load % Pharma contribution
52645-53-1	Permethrin	PCP	35.10%	
112-80-1	oleanolic acid	PCP	11.10%	
57-10-3	hexadecaneic acid	PCP	6.82%	
544-63-8	tetradecaneic acid	PCP	4.96%	
206-44-0	Fluoranthene	Plastic additive	4.50%	
50-28-2	17b-Estradiol	Pharma	3.63%	3.63%
112-18-5	N,N-Dimethyldodecylamine	PCP	2.65%	
58-08-2	Caffeine	Food product	2.21%	
91161-71-6	Terbinafine	Pharma	2.16%	2.16%
120-83-2	2,4-Dichlorophenol	Plastic additive	1.47%	
93413-69-5	Venlafaxine	Pharma	1.30%	1.30%
83905-01-5	Azithromycin	Pharma	1.26%	1.26%
111991-09-4	Nicosulfuron	Pesticide	1.24%	
1404-90-6	Vancomycin2H	Pharma	1.24%	1.24%
3380-34-5	Triclosan	PCP	1.18%	
65277-42-1	Ketoconazole	Pharma	1.07%	1.07%
138261-41-3	Imidacloprid	Pesticide	1.00%	
15687-27-1	Ibuprofen	Pharma	0.97%	0.97%
120068-37-3	Fipronil	Pesticide	0.79%	
79617-96-2	Sertraline	Pharma	0.75%	0.75%
27176-93-8	nonylfenoldiethoxylaat	PCP	0.61%	
80214-83-1	Roxithromycin	Pharma	0.57%	0.57%
85721-33-1	Ciprofloxacin	Pharma	0.57%	0.57%
129-00-0	Pyrene	Plastic additive	0.56%	
5466-77-3	- 2EthylHexyl4-methoxycinnamate	PCP	0.53%	
120-40-1	Lauryl diethanolamide	PCP	0.52%	
57808-66-9	Domperidone	Pharma	0.49%	0.49%
15545-48-9	Chlorotoluron	Pesticide	0.43%	
1071-83-6	Glyphosate	Pesticide	0.39%	
28179-44-4	joxitalaminoic acid	Pharma	0.34%	0.34%
72490-01-8	Fenoxycarb	Household product	0.33%	
117-81-7	Di(2-ethylhexyl)phthalate (DEHP)	Plastic additive	0.33%	
2465-59-0	Oxipurinol	Pharma	0.31%	0.31%
131929-60-7	Spinosyn A	Pesticide	0.30%	
846-49-1	Lorazepam	Pharma	0.29%	0.29%
118-42-3	Hydroxychloroquine	Pharma	0.26%	0.26%

CAS Number	Substance	Assigned Sector	Toxic load % contribution	Toxic load % Pharma contribution
139755-83-2	Sidenafil	Pharma	0.25%	0.25%
15307-86-5	Diclofenac	Pharma	0.24%	0.24%
2642-71-9	Ethyl azinphos	Pesticide	0.21%	
28159-98-0	Cybutryn (Irgarol)	Pesticide	0.21%	
66753-07-9	Terbuthylazine-2-hydroxy	Pesticide	0.21%	
846-50-4	Temazepam	Pharma	0.20%	0.20%
78649-41-9	Iomeprol	Pharma	0.20%	0.20%
108-95-2	fenol	Pesticide	0.18%	
54-31-9	Furosemide	Pharma	0.18%	0.18%
486-66-8	Daidzein	Other	0.16%	
330-54-1	Diuron		0.16%	
47221-31-8	Dodecylbenzenesulfonic acid	PCP	0.16%	
120067-83-6	Fipronil sulfide	Pesticide	0.16%	
60-54-8	Tetracycline	Pharma	0.12%	0.12%
94-75-7	2,4-D (Dichlorophenoxyacetic acid)	Pesticide	0.12%	
78-42-2	Tris(2-ethylhexl)phosphate	Plastic additive	0.11%	
96829-58-2	Orlistat	Pharma	0.10%	0.10%
128-37-0	butylhydroxytoluene (BHT)	PCP	0.10%	
1634-04-4	methyl-tertiair-butylether	Other	0.10%	
94-74-6	MCPA	Pesticide	0.09%	
25057-89-0	Bentazone	Pesticide	0.09%	
7311-30-0	N-Methyldodecylamine		0.08%	
584-79-2	Allethrin	Household product	0.08%	
333-41-5	Diazinon	Pesticide	0.08%	
23893-13-2	anhydro-erythromycine	Pharma	0.08%	0.08%
256-96-2	Iminostilbene	Pharma	0.08%	0.08%
191-24-2	Benzo[ghi]perylene		0.07%	
84-69-5	diisobutylftalaat	Plastic additive	0.06%	
90729-43-4	Ebastin	Pharma	0.06%	0.06%
120-72-9	indol	PCP	0.06%	
93-65-2	Mecoprop	Pesticide	0.06%	
34256-82-1	Acetochlor	Pesticide	0.06%	
604-75-1	Oxazepam	Pharma	0.06%	0.06%
121552-61-2	Cyprodinil	Pesticide	0.06%	
81403-80-7	alfuzosin	Pharma	0.06%	0.06%
147536-97-8	Bosentan	Pharma	0.06%	0.06%
22916-47-8	Miconazole	Pharma	0.05%	0.05%
92-87-5	Benzidine	Plastic additive	0.05%	

CAS Number	Substance	Assigned Sector	Toxic load % contribution	Toxic load % Pharma contribution
205-99-2	benzo(b)fluoranthene	Other	0.05%	
59277-89-3	Acyclovir	Pharma	0.05%	0.05%
103-90-2	Acetaminophen	Pharma	0.05%	0.05%
55268-75-2	Cefuroxime	Pharma	0.05%	0.05%
58-73-1	Diphenhydramine	Pharma	0.05%	0.05%
30223-73-5	EDDP	Pharma	0.05%	0.05%
100-97-0	Methenamine	Pharma	0.05%	0.05%
615-22-5	2-methylthiobenzothiazole	Household product	0.04%	
112-75-4	N,N-Dimethyltetradecylamine	PCP	0.04%	
39562-70-4	Nitrendipin	Pharma	0.04%	0.04%
519-09-5	Benzoylecgonin	Other	0.04%	
51146-55-5	2-hydroxyibuprofen	Pharma	0.04%	0.04%
83881-51-0	Cetirizine	Pharma	0.04%	0.04%
886-50-0	Terbutryn	Pesticide	0.04%	
140-66-9	(4-(1,1',3,3'-tetramethylbutyl)-phenol)	Plastic additive	0.04%	
76-73-3	Secobarbital	Pharma	0.04%	0.04%
80-05-7	Bisphenol A	Plastic additive	0.03%	
81334-34-1	Imazapyr	Pesticide	0.03%	
26787-78-0	Amoxicilin	Pharma	0.03%	0.03%
95-14-7	1H-Benzotriazole	Other	0.03%	
94-62-2	Piperine	PCP	0.03%	
25812-30-0	Gemfibrozil	Pharma	0.03%	0.03%
1120-24-7	N,N-Dimethyldecylamine	Other	0.03%	
66215-27-8	Cyromazine	Pesticide	0.03%	
84449-90-1	Raloxifene	Pharma	0.03%	0.03%
66357-35-5	Ranitidine	Pharma	0.03%	0.03%
153719-23-4	Thiamethoxam	Pesticide	0.03%	
56038-13-2	Sucralose		0.03%	
69-72-7	Salycilic acid	Pharma	0.03%	0.03%
100-88-9	Cyclamate	Pesticide	0.03%	
657-24-9	Metformin	Pharma	0.03%	0.03%
79902-63-9	Simvastatin	Pharma	0.03%	0.03%
564-25-0	Doxycycline	Pharma	0.03%	0.03%
50-48-6	Amitriptyline	Pharma	0.03%	0.03%
10605-21-7	Carbendazim	Pesticide	0.03%	
10540-29-1	Tamoxifen	Pharma	0.02%	0.02%
91-44-1	7-Diethylamino-4-methylcoumarin	PCP	0.02%	
723-46-6	Sulfamethoxazole	Pharma	0.02%	0.02%

CAS Number	Substance	Assigned Sector	Toxic load % contribution	Toxic load % Pharma contribution
111988-49-9	Thiacloprid	Pesticide	0.02%	
27619-97-2	6:2 fluorotelomer sulfonic acid	Plastic additive	0.02%	
81-07-2	Saccharin		0.02%	
101-20-2	Triclocarban	PCP	0.02%	
207-08-9	Benzo(k)fluoranthene	Other	0.02%	
70458-96-7	Norfloxacin	Pharma	0.02%	0.02%
4065-45-6	Benzophenone-4	PCP	0.02%	
53179-11-6	Loperamide	Pharma	0.02%	0.02%
210880-92-5	Clothianidin	Pesticide	0.02%	
69-53-4	Ampicillin	Pharma	0.02%	0.02%
53-86-1	Indometacin	Pharma	0.02%	0.02%
66108-95-0	Iohexol	Pharma	0.02%	0.02%
23593-75-1	Clotrimazole	Pharma	0.02%	0.02%
60-51-5	Dimethoate	Pesticide	0.02%	
5786-21-0	Clozapine	Other	0.02%	
108-91-8	Cyclohexylamine	Pharma	0.02%	0.02%
218-01-9	chrysene	Plastic additive	0.02%	
102-06-7	1,3-Diphenylguanidine	Plastic additive	0.02%	
108-38-3	1,3-xylene	Other	0.02%	
1222-05-5	Galaxolide	PCP	0.01%	
120068-36-2	Fipronil sulfone	Pesticide	0.01%	
38083-17-9	climbazole	PCP	0.01%	
33665-90-6	Acesulfame	Food product	0.01%	
106700-29-2	Pethoxamid	Pesticide	0.01%	
58955-93-4	trans-10,11-dihydroxy-10,11-dihydrocarbazepine	Pharma	0.01%	0.01%
5915-41-3	Terbutylazine	Pesticide	0.01%	
298-46-4	carbamazepine	Pharma	0.01%	0.01%
57-83-0	Progesterone	Pharma	0.01%	0.01%
73334-07-3	Iopromide	Pharma	0.01%	0.01%
16287-71-1	Benzyldimethyltetradecylammonium	Household product	0.01%	
58-55-9	Theophyllin	PCP	0.01%	
108-88-3	toluene	Other	0.01%	
47324-98-1	Denatonium	Household product	0.01%	
60142-96-3	Gabapentin	Pharma	0.01%	0.01%
62-53-3	aniline	Other	0.01%	
24280-93-1	Mycophenolic acid	Pharma	0.01%	0.01%
1951-25-3	Amiodarone	Pharma	0.01%	0.01%
56211-40-6	Torasemide	Pharma	0.01%	0.01%

CAS Number	Substance	Assigned Sector	Toxic load % contribution	Toxic load % Pharma contribution
26093-31-2	7-Amino-4-methylcoumarin	Other	0.01%	
28291-75-0	N-Cyclohexyl-2-benzothiazole-amine	Plastic additive	0.01%	
93479-97-1	Glimepiride	Pharma	0.01%	0.01%
525-66-6	Propanolol	Pharma	0.01%	0.01%
27203-92-5	Tramadol	Pharma	0.01%	0.01%
86386-73-4	Fluconazole	Pharma	0.01%	0.01%
122-80-5	4'-Aminoacetanilide	Other	0.01%	
31431-39-7	Mebendazole	Pharma	0.01%	0.01%
335-67-1	Perfluorooctanoic acid (PFOA)	Plastic additive	0.01%	
		TOTAL	99%	18%