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Predicting Pollutant Toxicity of over-the-counter (OTC) Pain Killers (Analgesic) Pharmaceutical Drug

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ABSTRACT

Over-the-counter (OTC) pain killers, while essential for managing discomfort, can pose significant environmental risks if improperly disposed of. This study aimed to evaluate the potential pollutant toxicity of commonly used analgesic drugs. EcoSAR, a quantitative structure-activity relationship (QSAR) model, was employed to predict the aquatic toxicity of these compounds based on their chemical structures. A diverse set of analgesic drugs was analyzed, including acetaminophen, ibuprofen, aspirin, and other (in total 19 class of drugs). The results in the form of LC_{50} revealed varying levels of toxicity among the studied compounds, with some demonstrating significant potential to harm aquatic organisms. The findings underscore the importance of responsible drug disposal and highlight the need for further research to develop effective strategies for mitigating the environmental impact of OTC pain killers.

Keywords: analgesic, EcoSAR, predicted toxicity,

INTRODUCTION

Over-the-Counter (OTC) painkillers, also known as analgesics, are a class of medications that can be purchased without a prescription. They are commonly used to alleviate pain from various sources, such as headaches, muscle aches, and arthritis, and are often found in medicine cabinets. OTC painkillers are divided into two primary classes: non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. NSAIDs are used to alleviate pain and inflammation and can be further classified into non-selective NSAIDs, such as ibuprofen and aspirin, and COX-2 selective NSAIDs, such as celecoxib (Moore et al., 2015). Acetaminophen, while not an NSAID, is another widely used OTC analgesic that primarily reduces pain and fever, generally being gentler on the stomach than NSAIDs (Ayoub, 2021).

NSAIDs work by inhibiting the production of prostaglandins, which are substances in the body that cause inflammation, pain, and fever. Non-selective NSAIDs target both COX-1 and COX-2 enzymes, leading to a wider range of effects, including stomach irritation (Gunaydin & Bilge, 2018). In contrast, COX-2 selective NSAIDs primarily target COX-2 enzymes, which are involved in inflammation but not in stomach protection, thus reducing the risk of stomach ulcers compared to non-selective NSAIDs. Acetaminophen, on the other hand,

is not an NSAID and works primarily by reducing pain and fever, making it generally gentler on the stomach than NSAIDs (Wongrakpanich et al., 2018).

Despite their widespread use, the environmental impact of these drugs has become a growing concern. Pharmaceutical residues, including those from NSAIDs and acetaminophen, have been detected in various aquatic ecosystems, raising questions about their potential toxicity to aquatic organisms. These compounds can enter the environment through various pathways, including improper disposal, wastewater treatment plant effluents, and agricultural runoff (Hejna et al., 2022).

In silico Ecological Structure-Activity Relationship (ECOSAR) models serve as valuable tools for predicting the toxicity of OTC painkillers, including analgesic pharmaceutical drugs. These computational methods leverage existing chemical data to assess the potential environmental impact of pharmaceuticals, providing insights into their toxicity to aquatic organisms and other non-target species. By utilizing in silico ECOSAR, researchers can efficiently screen large numbers of compounds, identify hazardous substances, and prioritize them for further experimental testing (Zhou et al., 2021). This approach not only accelerates the risk assessment process but also enhances our understanding of how various analgesics may affect ecosystems, facilitating more informed decision-making in drug development and regulatory frameworks (Hemmerich & Ecker, 2020).

The aim of this article is to systematically evaluate the environmental toxicity of over-the-counter (OTC) painkillers, specifically focusing on their impact on aquatic ecosystems. By employing in silico ECOSAR models, this study seeks to identify and quantify the potential risks associated with commonly used analgesics, including both NSAIDs and acetaminophen. Through this analysis, the research intends to highlight the importance of understanding the ecological consequences of pharmaceutical residues in the environment. Ultimately, the findings aim to inform policymakers and stakeholders about the necessity for improved waste management practices and regulatory measures to mitigate the environmental risks posed by these widely used medications.

METHODS

Selection of OTC Pain Killers

This study focuses on a range of commonly used over-the-counter (OTC) painkillers, specifically non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. A comprehensive literature review was conducted to identify these analgesics and gather relevant data on their chemical structures and known environmental impacts. The selected analgesics for this research include:

1. Diclofenac
2. Diflunisal
3. Etodolac
4. Fenoprofen
5. Flurbiprofen
6. Ibuprofen
7. Indomethacin
8. Ketoprofen

9. Ketorolac
10. Mefenamic acid
11. Meloxicam
12. Nabumetone
13. Naproxen
14. Oxaprozin
15. Piroxicam
16. Sulindac
17. Tolmetin
18. Celecoxib
19. Acetaminophen

These selected analgesics represent a diverse group of medications commonly utilized for pain relief, each with distinct mechanisms of action and profiles for efficacy and safety. Understanding the environmental toxicity of these widely used drugs is essential, as their residues can accumulate in aquatic ecosystems, potentially affecting local wildlife and water quality. By focusing on this range of OTC painkillers, this study aims to elucidate the potential ecological risks associated with their use and disposal.

Data Collection

Chemical data for the selected OTC painkillers were sourced from reputable databases, such as the PubChem, and the US EPA's ECOSAR database. Information on molecular weight, log P (partition coefficient), and other physicochemical properties was collected to facilitate the toxicity predictions.

In Silico Toxicity Prediction

In silico Ecological Structure-Activity Relationship (ECOSAR) models were used to predict the ecotoxicity of the selected analgesics. The ECOSAR software allows for the estimation of toxicity to various aquatic organisms, including fish, invertebrates, and algae. Each compound was analyzed using the ECOSAR model to generate predicted toxicity values (e.g., EC50 and LC50).

Risk Characterization

The predicted toxicity values were compared to established environmental quality standards (EQS) to assess potential risks to aquatic ecosystems. Risk characterization involved calculating the risk quotient (RQ) for each compound, which was determined by dividing the predicted environmental concentration (PEC) (assumed 1 mg/L) by the predicted no-effect concentration (PNEC) (Welch et al., 2023). Risk Quotient (RQ) using the formula:

$$RQ = \frac{PEC}{PNEC}, \text{ where } PNEC = \frac{LC50}{Assessment\ Factor}$$

Interpretation of Results

The results were interpreted to identify patterns and trends in the toxicity of OTC painkillers. The findings were discussed in the context of existing literature, emphasizing the implications for environmental health and regulatory practices.

Risk Quotient (RQ) Interpretation (Raimondo & Forbes, 2022):

RQ < 0.1 : Insignificant Risk: The predicted environmental concentration (PEC) is much lower than the predicted no-effect concentration (PNEC). This indicates minimal concern for ecological impacts.

RQ 0.1 – 1.0 : Low Risk: The PEC is below the PNEC, suggesting a low likelihood of adverse effects on aquatic organisms. While there may be some exposure, it is generally considered acceptable.

RQ 1.0 – 10.0 : Moderate Risk: The PEC is approaching or exceeds the PNEC, indicating a moderate risk of adverse effects. Further investigation may be warranted, and management strategies should be considered.

RQ > 10.0 : High Risk: The PEC significantly exceeds the PNEC, suggesting a high risk of adverse effects on aquatic ecosystems. Immediate action or regulatory measures may be necessary to mitigate risks.

Reporting and Recommendations

The final results were compiled into a comprehensive report outlining the predicted toxicity of each analgesic and providing recommendations for future research, regulatory considerations, and potential mitigation strategies to reduce environmental exposure

Results and discussion

Structure Preparation

The in silico ECOSAR analysis provided predicted toxicity values for each selected OTC painkiller. The results indicated varying levels of toxicity across the different compounds, with LC50 values reflecting their potential impact on aquatic organisms. In total 19 structures of OTC painkiller were prepared in SMILES structure format, to be ready processed with ECOSAR.

Predicted Toxicity Values

To provide a comprehensive overview of the predicted toxicity of the selected OTC painkillers, the following table summarizes the key data obtained from the ECOSAR predictions (Table 1). This includes the log Kow values, water solubility, LC50 values for fish, and the corresponding Risk Quotient (RQ) calculations for each analgesic. By examining this data, we can better understand the relative ecological risks associated with these commonly used medications.

Table 1. Physical Properties of OTC Painkiller Compounds

No	Name	Log Kow	Water Solubility (mg/L)
1	Diclofenac	4.0157	4.5183
2	Diflunisal	4.4095	15.858
3	Etodolac	3.9264	10.279
4	Fenoprofen	3.9023	166.09
5	Flurbiprofen	3.8104	15.426
6	Ibuprofen	3.7931	53.62
7	Indomethacin	4.2269	2.8207
8	Ketoprofen	3.0001	208.86
9	Ketorolac	2.3208	297.77
10	Mefenamic acid	5.2784	0.032861
11	Meloxicam	3.5025	0.54427
12	Nabumetone	3.2208	72.811
13	Naproxen	3.1029	56.467
14	Oxaprozin	4.0353	4.1717
15	Piroxicam	2.5775	4.402
16	Sulindac	4.2777	10.94
17	Tolmetin	2.5629	115.33
18	Celecoxib	3.4742	3.2961
19	Acetaminophen	0.2685	4189.8

The following Table 2. presents the predicted toxicity values (LC50) for the selected OTC painkiller compounds, derived from the ECOSAR analysis. These values indicate the concentration at which 50% of the test organisms (in this case, fish) are expected to be affected by each compound. Understanding these predicted toxicity levels is crucial for assessing the potential ecological risks associated with the use of these medications in aquatic environments. The data not only highlights the relative toxicity of each analgesic but also serves as a foundation for further risk assessment and management considerations.

Table 2. Predicted Toxicity (LC_{50}) of OTC Painkiller Compounds

OTC Painkiller	Lethal Concentration 50 (mg/L)		
	Organism		
	Daphnid (48h)	Fish (96h)	Green Algae (96h)
Acetaminophen - Neutral Organics	2.157.2	4457.7	829.7
Acetaminophen - Amides	1.198.3	948.0	61.2
Acetaminophen - Phenol amines	0.9	15.5	2.2
Acetaminophen - Phenols	63.3	319.6	378.2
Celecoxib - Neutral Organics	9.7	14.9	12.6
Celecoxib - Amides	5.9	7.5	1.6
Celecoxib - Pyrazoles/Diazoles	3.2	0.7	0.4
Diclofenac - Neutral Organics	25.8	37.7	41.4
Diflunisal - Neutral Organics	10.0	14.1	18.7
Diflunisal - Phenols	9.7	7.5	10.4
Etodolac - Neutral Organics	29.8	43.9	46.3

Etodolac - Pyrroles/Diazoles	13.0	1.9	1.8
Fenoprofen - Neutral Organics	26.4	38.9	40.6
Flurbiprofen - Neutral Organics	31.9	47.5	47.4
Ibuprofen - Neutral Organics	27.8	41.6	41.1
Indomethacin - Neutral Organics	20.5	29.4	35.7
Indomethacin - Pyrroles/Diazoles	10.7	1.2	1.6
Ketoprofen - Neutral Organics	164.5	264.1	179.5
Ketorolac - Neutral Organics	631.8	1.080.2	531.9
Ketorolac - Pyrroles/Diazoles	107.0	66.5	8.8
Mefenamic acid - Neutral Organics	1.7	2.3	4.5
Meloxicam - Neutral Organics	8.4	12.9	11.1
Meloxicam - Acrylamides	3.9	1.4	0.2
Meloxicam - Amides	5.1	6.6	1.4
Meloxicam - Vinyl/Allyl/Propargyl Alc.	5.4	2.4	0.1
Nabumetone - Neutral Organics	9.5	15.0	11.3
Naproxen - Neutral Organics	121.5	193.3	137.9
Oxaprozin - Neutral Organics	24.5	35.8	39.8
Piroxicam - Neutral Organics	49.4	82.5	45.9
Piroxicam - Acrylamides	11.6	4.2	0.3
Piroxicam - Amides	29.2	32.8	4.9
Piroxicam - Vinyl/Allyl/Propargyl Alc.	10.5	4.3	0.3
Sulindac - Neutral Organics	18.5	26.4	32.8
Tolmetin - Neutral Organics	394.7	659.9	364.5
Tolmetin - Pyrazoles/Diazoles	77.1	38.6	6.9

The data presented in Table 2 illustrate the predicted toxicity (LC50) values for the OTC painkiller compounds, highlighting the varying levels of potential impact on aquatic organisms. These toxicity values serve as a critical component for further risk assessment.

Risk Quotient (RQ) Analysis

To evaluate the ecological risks associated with these analgesics, the next table provides the calculated Risk Quotient (RQ) for each compound. The RQ is derived by comparing the predicted environmental concentration (PEC) to the predicted no-effect concentration (PNEC), offering insight into the relative safety or risk of each substance in the environment. This analysis is essential for understanding which painkillers may pose significant threats to aquatic ecosystems and guiding future research and regulatory efforts.

Table 3. Risk Quotient (RQ) Analysis of OTC Painkiller Compounds

	Daphnid (48h)	Fish (96h)	Green Algae (96h)
Acetaminophen - Neutral Organics	0.00	0.00	0.00
Acetaminophen - Amides	0.00	0.00	0.02
Acetaminophen - Phenol amines	1.14	0.06	0.45
Acetaminophen - Phenols	0.02	0.00	0.00
Celecoxib - Neutral Organics	0.10	0.07	0.08
Celecoxib - Amides	0.17	0.13	0.64
Celecoxib - Pyrazoles/Diazoles	0.31	1.39	2.57
Diclofenac - Neutral Organics	0.04	0.03	0.02
Diflunisal - Neutral Organics	0.10	0.07	0.05
Diflunisal - Phenols	0.10	0.13	0.10
Etodolac - Neutral Organics	0.03	0.02	0.02
Etodolac - Pyrroles/Diazoles	0.08	0.51	0.55
Fenoprofen - Neutral Organics	0.04	0.03	0.02
Flurbiprofen - Neutral Organics	0.03	0.02	0.02
Ibuprofen - Neutral Organics	0.04	0.02	0.02
Indomethacin - Neutral Organics	0.05	0.03	0.03
Indomethacin - Pyrroles/Diazoles	0.09	0.82	0.61
Ketoprofen - Neutral Organics	0.01	0.00	0.01
Ketorolac - Neutral Organics	0.00	0.00	0.00
Ketorolac - Pyrroles/Diazoles	0.01	0.02	0.11
Mefenamic acid - Neutral Organics	0.58	0.44	0.22
Meloxicam - Neutral Organics	0.12	0.08	0.09
Meloxicam - Acrylamides	0.25	0.72	5.42
Meloxicam - Amides	0.20	0.15	0.72
Meloxicam - Vinyl/Allyl/Propargyl Alc.	0.19	0.41	8.65
Nabumetone - Neutral Organics	0.10	0.07	0.09
Naproxen - Neutral Organics	0.01	0.01	0.01
Oxaprozin - Neutral Organics	0.04	0.03	0.03
Piroxicam - Neutral Organics	0.02	0.01	0.02
Piroxicam - Acrylamides	0.09	0.24	3.46
Piroxicam - Amides	0.03	0.03	0.20
Piroxicam - Vinyl/Allyl/Propargyl Alc.	0.10	0.23	3.80
Sulindac - Neutral Organics	0.05	0.04	0.03
Tolmetin - Neutral Organics	0.00	0.00	0.00
Tolmetin - Pyrazoles/Diazoles	0.01	0.03	0.15

RQ Value Interpretation:
High Risk: RQ > 10.0
Moderate Risk: RQ 1.0 – 10.0
Low Risk: RQ 0.1 – 1.0
Insignificant Risk: RQ < 0.1

The Risk Quotient (RQ) analysis presented in the table provides critical insights into the potential ecological risks associated with the selected OTC painkiller compounds. The calculated RQ values indicate the relative safety or risk of each analgesic based on their

predicted environmental concentrations compared to their no-effect levels. As seen in the Table 3, compounds with RQ values below 1 suggest a low risk to aquatic organisms, while those with values above 1 indicate potential concerns for environmental health. This analysis underscores the importance of responsible use and disposal of these medications, as even low concentrations can have cumulative effects on aquatic ecosystems.

The findings highlight the need for ongoing monitoring and further research to fully understand the implications of pharmaceutical residues in the environment. Additionally, these results can inform regulatory decisions aimed at mitigating the ecological risks posed by OTC painkillers.

CONCLUSION

This study evaluated the environmental toxicity of selected over-the-counter (OTC) painkillers using in silico ECOSAR models to predict toxicity values and assess potential ecological risks. The results demonstrated varying levels of predicted toxicity (LC50) among the analgesics, highlighting the need for careful consideration of their environmental impacts.

The Risk Quotient (RQ) analysis revealed that while some compounds posed low risks to aquatic organisms, others may warrant further scrutiny due to their potential ecological effects. The findings emphasize the importance of understanding the environmental implications of pharmaceutical residues, particularly in aquatic ecosystems where even low concentrations can disrupt ecological balance.

Overall, this research contributes to the growing body of evidence regarding the ecological risks associated with OTC painkillers and underscores the necessity for improved management and regulatory strategies to mitigate these risks. Future studies should focus on empirical assessments of environmental concentrations and the cumulative effects of multiple pharmaceuticals to develop comprehensive risk management frameworks.

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