Toxicological profile of porphyrin derivative from petroleum

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Abstract. Porphyrins and chlorins are both tetrapyrrole macrocycles, but chlorins are partially hydrogenated porphyrins, meaning they have one pyrroline ring instead of four pyrrole rings. Porphyrins are the foundational structure, while chlorins are derived from them through hydrogenation. Chlorophylls are the primary pigments used by photosynthetic organisms to absorb light, transfer energy, and initiate charge separation, a process essential for life. The CompTox Chemistry Dashboard is a tool for predicting intrinsic chemical and toxicological properties of a single, isolated molecule in a standardized environment. The goal is to use the US Environmental Protection Agency's (EPA) CompTox Chemicals Dashboard to predict the toxicological properties of a chlorin (porphyrin derivative) by inputting its chemical information and leveraging the platform's predictive tools. This will help assess the compound's potential hazards by using the Dashboard's integrated data on chemistry, toxicity, and exposure for a vast number of chemicals.

1 Introduction

Porphyrinoids are essential, colorful tetrapyrrole derivatives in nature, playing vital roles in processes like oxygen transport (heme), photosynthesis (chlorophyll), and energy metabolism. Other examples include vitamin B12 (cobalamin) and coenzyme F430. They are derived from a common precursor and have significant applications in medicine, such as photodynamic therapy and diagnosis [1,2]. Porphyrin-based derivatives are widely used due to their versatility and stability, stemming from the "pigments of life" research pioneered by Battersby and co-workers. These materials have unique photoelectrochemical properties, making them valuable for applications ranging from medicine to materials science, including roles in photosynthesis, oxygen transport, and photocatalysis [3,4]. Porphyrins are a class of naturally occurring organic compounds that are essential in biological systems, such as the heme in hemoglobin and chlorophyll in plants [5].

Porphyrins are naturally occurring organic compounds with four interconnected pyrrole rings that are important in biology, appearing in heme, chlorophyll, and cytochromes. They have unique optical properties, including strong light absorption in the visible spectrum, which gives them their name (from the Greek word for purple) and makes them appear as colored pigments. Porphyrins are chemically stable and play crucial roles in functions like

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oxygen transport, photosynthesis, and as cofactors in enzymes [6]. Chlorins are a class of heteromacrocyclic organic compounds officially named 2,3-dihydroporphyrin or 2,3-dihydroporphine. The main application for both porphyrins (like porfimer sodium) and chlorins (like chlorin e6) is in photodynamic therapy (PDT) for cancer and age-related macular degeneration, as well as for antibacterial/antiparasitic treatments. They are also explored for use in medical imaging (theranostics) [6]. The statement describes porphyrins and metalloporphyrins, explaining that while porphyrins are often dark purple and fluorescent, their color changes when a metal ion is inserted to form a metalloporphyrin [7]. Chlorins have very similar properties to porphyrins, but their UV-visible spectra show a key difference due to the reduced aromaticity of one pyrrole ring [8].

Porphyrin derivatives, specifically heme and chlorophylls, are the most abundant and biologically crucial natural tetrapyrrole pigments. These naturally occurring molecules were the primary sources through which scientists understood the fundamental porphyrin macrocyclic structure and its vital role in biological functions like oxygen transport and photosynthesis [9]. Porphyrins have evolved from being purely a biological curiosity to having a wide range of modern technological and medical applications (Dye-Sensitized Solar Cells, Preparation of Molecular Devices, and Disease Diagnosis and Therapy) [10-12].

The fundamental biological roles of porphyrins were precisely what led scientists to explore their potential in human health, particularly concerning cancer. This natural affinity for cancer cells, combined with their inherent fluorescent and photosensitizing properties, made them ideal candidates for investigation into cancer diagnosis and therapy [9].

Solutions to protect against chemical-related harm include government regulation (EPA, state, and international), enforcement of laws like the Clean Air Act and Clean Water Act, and industry efforts such as pollution control and waste reduction. The EPA, along with other agencies, sets standards, conducts research, provides technical assistance, and enforces laws through measures like fines and sanctions to safeguard public health and the environment. The Computational Toxicology (CompTox) Chemicals Dashboard is a U.S. EPA-hosted online tool that provides chemistry, toxicity, and exposure data for over one million chemicals. It helps scientists and decision-makers quickly evaluate compounds by providing data and models for identifying chemicals that need more testing and reducing animal testing. The dashboard includes information on chemical structures, experimental and predicted data, hazard assessments, and links to other relevant resources.

The goal is to use the US Environmental Protection Agency's (EPA) CompTox Chemicals Dashboard to predict the toxicological properties of a chlorin (porphyrin derivative) by inputting its chemical information and leveraging the platform's predictive tools. This will help assess the compound's potential hazards by using the Dashboard's integrated data on chemistry, toxicity, and exposure for a vast number of chemicals.

2 Materials and methods

2.1 Compound data

Porphyrins are a class of aromatic macrocyclic organic compounds, crucial in biological systems due to their role in light harvesting, electron transfer, and oxygen transport. Porphyrin derivatives, formed by modifying the basic porphyrin structure, expand their functional versatility and are widely used in various applications, including materials science and biomedicine (Figure 1) [13].

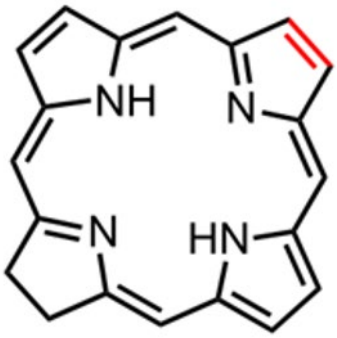


Fig. 1. The structure of a porphyrin derivative (chlorin).

2.2 The EPA's CompTox Chemicals Dashboard

The EPA's CompTox Chemicals Dashboard is a freely accessible web-based application and data hub providing public access to data associated with hundreds of thousands of chemical substances. It integrates data from other platforms, specifically PubChem and PubMed, via web services and visualization widgets. The data and predictive models within the Dashboard support the EPA's efforts to accelerate chemical hazard assessment and reduce the reliance on animal testing. The platform is continually updated with new data types, predictive models, and features to support environmental scientists and regulators [14].

3 Results and Discussion

A toxic endpoint accurately describes the observable, measurable result of a study that determines a substance's danger. Data from toxicity studies, such as those that determine toxic endpoints like LD_{50} or LC_{50} values, are fundamental for: Reporting toxicity, Hazard Classification and Labeling, Risk Assessment, and Guiding Further Research. Overall, this process ensures that the potential risks of chemical compounds to human health and the environment are appropriately identified and managed [14].

Toxic endpoints are generally categorized as acute or chronic, reflecting the duration of exposure and the timeframe over which effects are observed. Acute toxic endpoints are the results of short-term studies, typically lasting a few seconds to a week, resulting from a single or short series of high-concentration exposures. Chronic toxic endpoints are the results of long-term, repeated exposures to lower concentrations of a substance, often over a significant portion of an organism's lifespan (months or years). These endpoints focus on sublethal, cumulative, or delayed effects that may not be apparent in acute tests. The distinction between acute and chronic endpoints is vital for conducting relevant toxicity studies and for establishing appropriate safety guidelines and regulations [14].

The use of integrated approaches and consensus methods is a standard practice in computational toxicology when experimental data (for example, chlorin) is unavailable, allowing regulatory agencies and compliance groups to make informed decisions about potential hazards. The specific methods (Hierarchical clustering - HC, Single model - SM, Group contribution - GC, and Nearest neighbor - NN) are standard techniques used in Quantitative Structure-Activity Relationship (QSAR) modeling and read-across approaches.

Results of prediction (Endpoints) of chlorin by the EPA's CompTox Chemicals Dashboard are presented in Table 1.

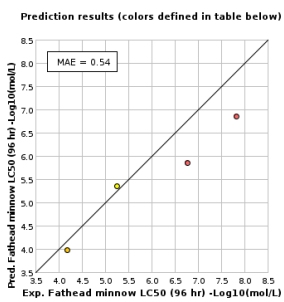
Table 1. Predicted results of toxicological endpoints for chlorin

Endpoints	Consensus	Model HC	Model SM	Model GC	Model NN
96 h Fathead minnow LC_{50}, mg/L	0.262	0.180	0.180	-	0.558
48 h *Daphnia magna* LC_{50}, mg/L	0.909	0.303	0.410	-	6.059
48 h *Tetrahymena pyriformis* IGC_{50}, mg/L	3.792	-	-	1.315	10.941
Oral rat LD_{50}, mg/kg	-	-	-	-	700.99
Bioconcentration factor	9.664	16.618	7.655	-	7.095
Developmental toxicity	false	false	-	-	true
Ames mutagenicity	false	false	-	-	false
Estrogen Receptor RBA	-	-	-	-	-
Estrogen Receptor Binding	-	-	-	-	-

The predictions strongly indicate that chlorin is highly toxic to aquatic life (fish and water fleas) at low concentrations. The compound appears to have moderate acute oral toxicity but is predicted to be non-mutagenic and likely negative for developmental toxicity (based on the consensus 'false' result, despite the 'true' from the Nearest Neighbor model). The data relies entirely on models, highlighting the need for experimental verification if this compound is to be widely used or regulated. The missing entries (−) indicate that those specific models did not generate a prediction for that endpoint.

For each toxicological endpoint model developed using computational methods like Quantitative Structure-Activity Relationships (QSAR) or machine learning, a training set and an external test set are defined. Comparing the predictions for a novel test chemical (chlorin) to the experimental data of the most similar chemical (analogue) in the training and external test set has been made (Tables 2-10).

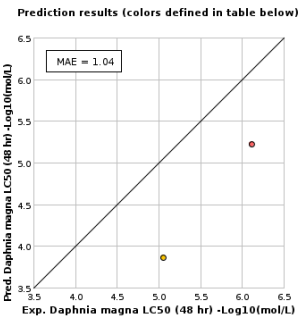
Table 2. Predicted Endpoint (96 h Fathead minnow, LC_{50}) of chlorin by method (Consensus).

End-point	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set	MA Error*	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set	MA Error *
96 h Fathead minnow LC_{50}, mg/L		Ent. set-0.48 Similar. Coeff. ≥ 0.5 (0.54)	If the most similar chemical available in the database scores less than 0.5, it means there are no close structural analogues with existing experimental data.	Ent. set-0 Similar. coeff ≥ 0.5 (0.00)

*__MAE__ – Mean absolute error in –Log10 (mol/L), Ent. set - Entire set, Similar. Coeff. - Similarity coefficient

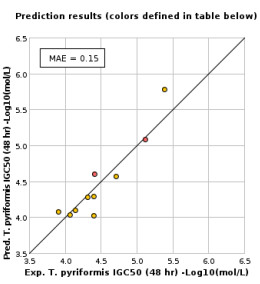
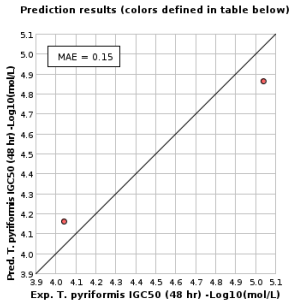
Toxicity predictions were made for the test compound (chlorin) relative to the Fathead minnow LC_{50} (96 h) from the Consensus method. Several (four) similar compounds were found in the database as a training set, based on which a prediction was made. Predictions for the test compound from an external test set were not made because there is no compound in it that exceeds the minimum similarity coefficient of 0.5.

Table 3. Predicted toxicological property (48 h *Daphnia magna*, LC_{50}) of chlorin by method (Consensus).

End-point	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set	MA Error*	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set	MA Error*
48 h *Daphnia magna* LC_{50}, mg/L	No similar compounds found for prediction	Ent. set-0 Similar. Coeff. ≥ 0.5 (0.00)		Ent. set-0.74 Similar. Coeff. ≥ 0.5 (1.04)

The test compound (chlorin) was predicted for *Daphnia magna* LC_{50} (48 h) using the Consensus method - 0.91 mg/L. There are no similar compounds in the training set to predict a similarity coefficient, while in the external test set, it is possible to predict.

Table 4. Predicted toxicological property (48 h *Tetrahymena pyriformis*, IGC_{50}) of chlorin by method (Consensus).

End-point	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set	MA Error*	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set	MA Error*
48 h *Tetrahymena pyriformis* IGC_{50}, mg/L		Ent. set-0.28 Similar. Coeff. ≥ 0.5 (0.15)		Ent. set-0.33 Similar. Coeff. ≥ 0.5 (0.15)

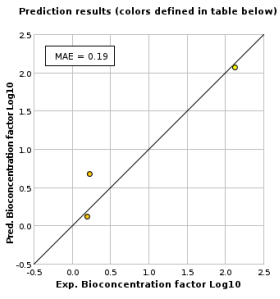
The test compound (chlorin) was predicted for *Tetrahymena pyriformis*, IGC_{50} (48h) using the Consensus method - 3.79 mg/L. A training set of ten compounds and an external test set of three compounds were formed with similar compounds with experimental data, based on which a prediction was made with a similarity coefficient greater than or equal to 0.5.

Table 5. Toxicological property prediction (oral rat, LD_{50})

End-point	**Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set**	**MA Error***	**Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set**	**MA Error***
Oral rat LD_{50}, mg/kg	No similar compounds found for prediction	Ent. set-0 Similar. Coeff. ≥ 0.5	No similar compounds found for prediction	Ent. set-0 Similar. Coeff. ≥ 0.5 (0.00)

The toxicity prediction of the test compound (chlorin) for oral rat LD_{50} was made only with the Nearest neighbor method, and a value of 705.521 mg/kg was obtained.

Table 6. Predicted toxicological property (Bioconcentration factor) of chlorin by method (Consensus).

End-point	**Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set**	**MA Error***	**Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set**	**MA Error***
Bioconcentration factor		Ent. set-0.42 Similar. Coeff. ≥ 0.5 (0.19)	If the most similar chemical available in the database scores less than 0.5, it means there are no close structural analogues with existing experimental data.	Ent. set-0 Similar. Coeff. ≥ 0.5 (0.00)

Prediction of the bioconcentration factor for the test compound (chlorin) was performed using the Consensus method with a result of 9.664. Three similar compounds with experimental data were found to predict the test compound, which had a similarity coefficient greater than or equal to 0.5. If the most similar chemical available in the database scores less than 0.5, it means there are no close structural analogues with existing experimental data.

Table 7. Predicted result for the toxicological property (Development toxicity)

End-point	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set	MA Error *	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set	MA Error*
Developmental toxicity	No similar compounds found for prediction	Concord. - 1.00 Sensit. - 1.00 Specif. - N/A	If the most similar chemical available in the database scores less than 0.5, it means there are no close structural analogues with existing experimental data.	Concord. - 0.80 Sensit. - 0.75 Specif. - 1.00

* Concord. – Concordance, Sensit. – Sensitivity, Specif. – Specificity.

Prediction of Development Toxicity of the test compound (chlorin) was performed using the Consensus method. In the training set, one similar compound was available, and a prediction using the external test set was not made.

Table 8. Predicted result for the toxicological property (Ames mutagenicity) of chlorin

End-point	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set	MA Error *	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set	MA Error*
Ames mutagenicity		Concord. -1.0 Sensit. - 1.0 Specif. - 1.0		Concord. - 0.90 Sensit. - 1.0 Specif. - 0.75

In the training set (ten similar compounds) and in the external test set (ten compounds), whose experimental data are of quality +/- or 0/1, are used to predict Ames mutagenicity. Predictions are made using the Consensus method.

Table 9. Predicted result for the toxicological property (Estrogen Receptor RBA) of chlorin

End-point	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set	MA Error*	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set	MA Error*
Estrogen Receptor RBA	No similar compounds found for prediction		No similar compounds found for prediction	

No predictions have been made for Estrogen Receptor RBA and Estrogen Receptor Binding. Experimental data for these toxicities are qualitative.

Table 10. Predicted result for the toxicological property (Estrogen Receptor Binding) of chlorin

End-point	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the training set	MA Error*	Comparing the predictions for a novel test chemical to the experimental data of the most similar chemical (analogue) in the external test set	MA Error*
Estrogen Receptor Binding	No similar compounds found for prediction		No similar compounds found for prediction	

4 Conclusion

Porphyrins are macrocyclic compounds that can be modified in a seemingly infinite number of ways. These derivatizations often have remarkable and unique properties that can be used in a variety of applications. Overall, porphyrins are an interesting, diverse, and versatile class of molecules that is constantly expanding. Due to the wide application of porphyrins, it is necessary to study the possible toxicological potential for human health and the environment. Computational or "in silico" methods (such as Quantitative Structure-Activity Relationships (QSAR), structural alerts, and read-across analysis) are used to predict the potential toxicity of chemicals based on their molecular structure and existing data from similar compounds.

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