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Toxicity focus is essential for Green Chemistry Adoption and sustainable product development

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ABSTRACT

'Green Chemistry Adoption' prescribes that companies must evaluate toxicity impact throughout the product development lifecycle, minimize the toxic waste generation, and use of toxic raw material. As more companies are adopting Green chemistry, there is a critical need to understand the toxicity of chemicals in terms of ecological and health impact. ViridisChem has built the most comprehensive toxicity database with over 90 million chemicals and 2.4 billion properties and has 10 times more toxicity data than any other chemical database available in the global market. Utilizing this information, it is developing products that can analyze any chemicals, even the new and postulated molecules, mixtures/formulations, and processes.

Using these tools, pharmaceutical, biochemical, agrochemical industries and the chemical suppliers can:

- Predict the toxicity of new molecules and their derivatives in real-time, thereby screen out the toxic drug targets, and avoid spending R&D time on them
- Avoid the use of toxic raw materials, and quickly find better and less toxic chemicals that satisfy the reaction specific requirements
- Fully understand the health, safety and ecological risks of toxic formulations, and find better formulations that offer the same benefits
- Avoid the use of cocktail of formulations that may be non-toxic individually, but become very potent when combined
- Define sustainable product development processes by avoiding toxic reagents during every step, and minimizing the toxic waste

1. Ideas behind the start-up

ViridisChem is the 3rd successful company founded by Neelam Vaidya, a 30-year veteran of the hi-tech and biotech industries, with the passion to provide solutions that can help companies worldwide to adopt sustainable product development.

The Pharmaceutical and biochemical industries have celebrated innovations over the past 12 years in the green chemistry space, like the awards offered by the EPA Green Chemistry Program "Presidential Green Chemistry Challenge Winners" (https://www.epa.gov/green-chemistry/presidential-green-chemistry-challenge-winners, 2017), where companies like Pfizer, Merck, BASF, Codexis, BristolMeyer Squibb, Roche, Eli Lilly, etc. were able to establish that adopting sustainable product development can save millions of dollars by avoiding wasted R&D effort in studying high-risk drug targets, and by minimizing the cost of toxic waste disposal. By paying attention to toxicity right from early discovery phase to product development phase, they were able to eliminate high-risk drug targets. By consciously selecting less toxic raw material and by avoiding the use of volatile organic compounds, they were able to reduce the amount of toxic waste by up to 90%. Ms. Vaidya wanted to find out why other companies were not adopting this practice. It seemed that with global competitive market, manufacturing cost-cutting would be any company's first priority.

She felt that if she could identify the problems and provide the

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solutions, she could help companies across the world move towards adoption of “Green Chemistry” and sustainable product development. Since toxic chemicals, mixtures and formulations are used within almost all sectors, it was also evident that these solutions will have a huge global addressable market and offer a tremendous revenue-generating opportunity.

After talking to leading researchers from companies from different sectors, the following main concerns were identified, and ViridisChem was formed to address these concerns

- Toxicity information of only 0.1% known chemicals is available, and 80% of Material Safety Datasheets are either incomplete or inaccurate. Tools that can provide the toxicity of every chemical and that can identify less toxic alternatives are needed.
- Keeping track of worldwide government regulations for compliance is becoming very difficult. Having to constantly change manufacturing processes as new toxic chemicals are being identified with increasingly restrictive usage thresholds is also very costly.
- Chemists/engineers who define manufacturing processes typically are not trained to understand toxicity data and need visual tools that can identify toxic chemicals within their processes and that can identify less toxic alternatives.
- Suppliers of mixtures and formulations do not like to disclose the ingredient information (specially the percent composition of the ingredients within the mixture) of their formulations and consider it to be their trade secret. But they are also not able to provide accurate toxicity implications, because measuring toxicity of mixtures and formulations is complex, and dependent on the reactivity among ingredients, as well as environmental factors. Models and tools that can accurately measure the mixture toxicity do not exist. As a result, Manufacturers and retailers are using formulations without fully understanding its toxicity.

ViridisChem is addressing these issues with sophisticated software products that are hosted on Cloud/SaaS platform, powered by Artificial Intelligence techniques, and supported by its own most comprehensive toxicity database. It is developing products that offer detailed toxicity evaluation of chemicals, mixture/formulations, materials, as well as per-step analysis of product development processes.

2. Contribution to green and sustainable chemistry

Government regulatory departments and product safety organizations are performing toxicity studies of commonly used suspected chemicals. But they have limited resources and so far, have only been able to release information on a few thousand chemicals (less than 0.05% of known chemicals). They are also shifting their focus from hazard assessment to risk assessment (http://chemsec.org/hazard-vs-risk-what-is-best-practice-when-assessing-chemicals/, 2016; https://www.ncbi.nlm.nih.gov/pubmed/379, 1815, 1991; https://www.epa.gov/sites/production/files/, 2014–12/documents/hhra-framework-final-, 2014.pdf, 2014) where rather than just focusing on the hazard properties of the chemical, exposure risk is also considered. This requires the toxicity evaluation of the chemical in terms of ecological, health and safety risks, while considering the amount of chemical being used (Fig. 1).

The ViridisChem toxicity database includes 48 physical and toxicological properties of 99% of known chemicals. It has built a software product called “Chemical Analyzer” that provides real-time toxicity evaluation of every chemical, even the new drug targets (to identify high risk drug targets and explore less toxic derivatives); find less toxic starting material based on scientist's specific reaction needs; and identify most global regulatory concerns about the target chemical. The toxicity evaluation is based on 44 different endpoints (see Fig. 2) defined by NSF/ANSI 355 standard (NSF/ANSI 355 Standard) and per United Nations, EPA, and EU-REACH guidelines that recommend comprehensive breakdown of ecological, health and safety hazards.

The company is also developing tools that will measure the toxicity of mixtures, formulations, materials, and processes. Using these tools, pharmaceutical, biochemical, agrochemical industries and the chemical suppliers can:

- Predict the toxicity of new molecules and their derivatives in real-time, thereby screen out the toxic drug targets, and avoid wasted R&D efforts
- Avoid the use of toxic raw materials, and quickly find better and less toxic chemicals that satisfy the reaction specific requirements
- Fully understand the health, safety and ecological risks of toxic formulations, and find better formulations that offer the same benefits
- Avoid the use of cocktails of formulations that may be non-toxic individually, but become very potent when combined
- Define sustainable product development processes by avoiding toxic reagents during every step, and minimizing the toxic waste

We have collected extensive experimental data from public and government sources, universities, regulatory lists, and now are receiving data from our strategic partners (large chemical suppliers).

Traditional Quantitative structure–activity relationship models (**QSAR** models) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5494643/, 2017) currently being used industry-wide are regression or classification models and their performance depends on two factors:

- Accuracy of the quantitative relationship defined between chemical's physicochemical properties and the biological activity being predicted
- Quantity and Quality or accuracy of the training and reference data used

Newer models that are based on Deep Learning artificial Neural Networks (http://www.bioinf.jku.at/publications/, 2016/fenvs-03–, 00080.pdf, 2016; https://doi.org/10, 1093/toxsci/kfy152, 2018) offer learning of all toxic effects in one neural network and thereby learning of highly informative chemical features. Accuracy of these models primarily depends on the quality of the data, and in order for these models to self-train, you need to feed in very large volume of data on diverse types of chemicals.

In short, no matter what type of prediction models you use, accuracy of their results mainly depends on the availability of large amount of accurate data.

By having access to large amount of experimental data, and by constantly curating our database using tools that automatically identify bad data and fix it, ViridisChem has the ability to offer highly accurate tox-prediction models, or train customers models for higher accuracy.

3. Roadblocks

Our goal is to be the “de-facto standard” for toxicity evaluation. This means that we must provide toxicity evaluation of every chemical, mixture, formulation and processes in a way that will be relevant for different sectors.

But to provide this, we must have access to the physical and functional properties of every chemical that exists.

We quickly realized that such a comprehensive database of chemicals with comprehensive toxicological properties did not exist. We also experienced that available databases had conflicting information for many chemicals, and serious curation efforts were needed to get consistent, trustworthy data. Therefore, we decided to build our own chemical database that we could trust and curate. By adopting this strategy, we were also able to avoid critical dependency on third-party partnerships in terms of access to the data, and the quality of the data.

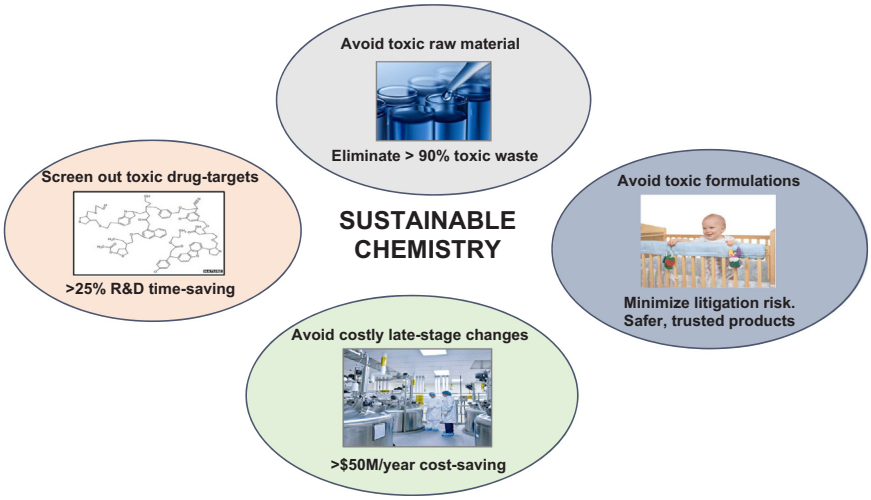


Fig. 1. Benefits of Sustainable Chemistry Adoption.

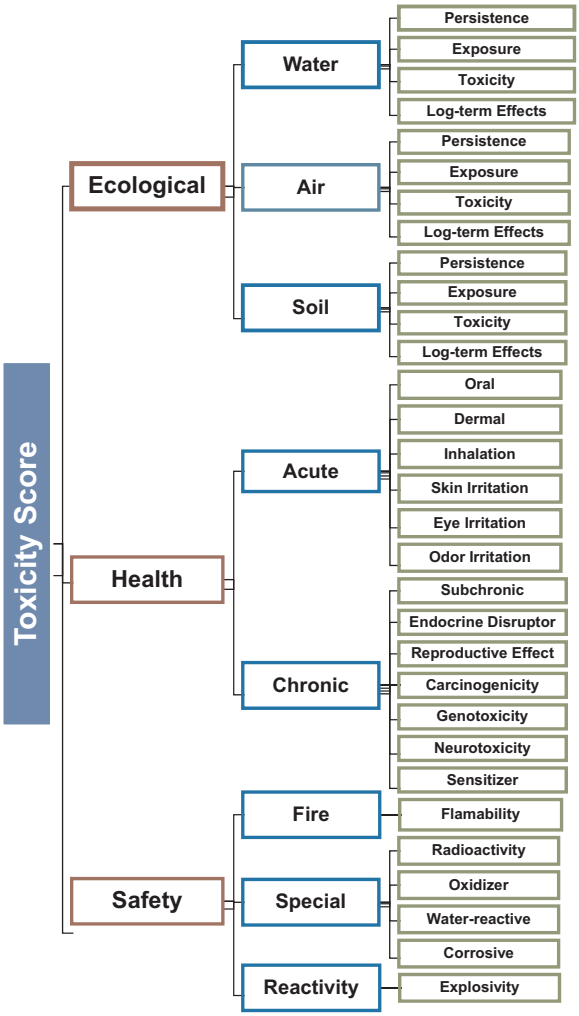


Fig. 2. Endpoints That Define Toxicity Per ANSI STD 355.

4. Our approach

ViridisChem has built the most comprehensive toxicity database with over 90 million chemicals and 2.4 billion properties. We have 10 times more toxicity data than any other chemical database available worldwide.

We have also built a powerful Cloud-SaaS (Software as a Service) software platform that can:

- Host or accommodate multi-tenant databases (e.g. ViridisChem toxicity database, customer's proprietary chemical database hosted on cloud platform, or within company's firewall, relational as well as cloud databases)
- Host toxicity prediction models developed by ViridisChem or customers

The platform in fact includes an artificial intelligence layer that learns from the execution of available models to offer increasingly accurate toxicity analysis of chemicals, mixtures and formulations.

Utilizing this platform, we offer the following software products on yearly subscription to companies worldwide:

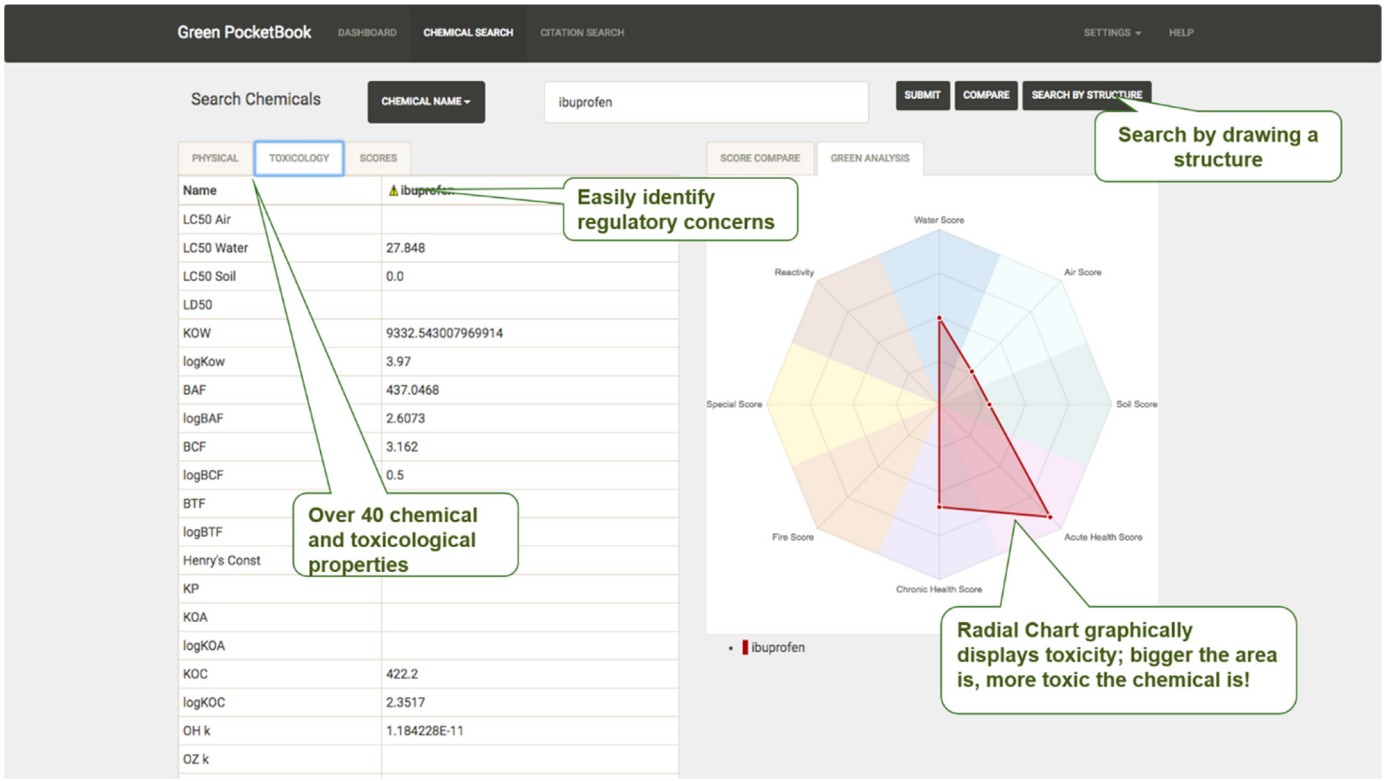
- Chemical Analyzer (commercially available): Provides comprehensive physical and toxicological properties of any known or unknown chemical, offers full GHS classification (https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev07/English/ST_SG_AC10_30_Rev7e.pdf, 2017) and identifies most US and international regulatory concerns along with the known toxic chemical's usage threshold defined by various US and international regulatory departments.

For discovery scientists within the pharmaceutical industry, it also performs real-time toxicity prediction of new drug targets and allows them to explore less toxic derivatives by simply tweaking the structure.

The tool also offers an “Advanced Search” feature, where the scientists can provide their specific reaction requirements (need specific functional group, specific melting-point/boiling-point value range, must avoid certain health issues, etc.); and receive a list of less toxic chemicals that match their requirements.

Using the physical and toxicological property values, along with available experimental data, Chemical analyzer utilizes proprietary algorithms to calculate the values of 44 different end-points (see Fig. 2) recommended by NSF-ANSI 355 standard (NSF/ANSI 355 Standard) as shown below, that together define the toxicity of the chemical.

Chemical's toxicity impact is measured in terms of ecological, health, and safety scores, and is shown visually; so that chemists and engineers can understand the information without needing any training. The product allows comparison among chemicals by showing the information side-by-side in a table, and by overlaying the toxicity area using transparency and color differentiation on the graph (see Fig. 3).



Name	ibuprofen
LC50 Air	
LC50 Water	27.848
LC50 Soil	0.0
LD50	
KOW	9332.543007969914
logKow	3.97
BAF	437.0468
logBAF	2.6073
BCF	3.162
logBCF	0.5
BTF	
logBTF	
Henry's Const	
KP	
KOA	
logKOA	
KOC	422.2
logKOC	2.3517
OH k	1.184228E-11
OZ k	

Fig. 3. ViridisChem Chemical Analyzer showing toxicity through shaded area.

Here is a snapshot of the product (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5494643/, 2017) (Fig. 3) showing the toxicity of the drug "Ibuprofen". Please note that the graph on the right quantifies the toxicity impact. The bigger the area, the more toxic the chemical is.

- Formulation Analyzer (under development): The product includes a platform and a set of applications. It will be used by all players within the consumer industry supply chain. The platform allows suppliers to securely input detailed ingredient information of mixture and formulations and create dynamic detailed reports without disclosing the ingredient details.

Suppliers can then share these reports in varying levels of details with manufacturers, retailers, or certifying agencies through role-based access levels. Manufacturers can refer to these reports to ensure global regulatory conformance, and to make sure that they are addressing the product's usage specific concerns and avoiding the acute and chronic health issues critical for the product's user community.

Manufacturers can also use this platform to aggregate the toxicity of all the mixtures and formulations involved in their product development to evaluate overall product toxicity. This transparency of information-sharing among suppliers and manufacturers enables productive communication to request improvements and offers competitive advantage to both the parties. (Fig. 4)

5. Factors of success

ViridisChem enjoys the first-in-market advantages, and has an opportunity to be the industry de-facto standard for toxicity analysis due to following factors:

- It has built proprietary AI powered algorithms, patent-pending technologies
- It owns the world's largest toxicity database with highly curated data
- ViridisChem is the only company offering off-the-shelf toxicity evaluation products that don't require training

We hope to partner with:

- Chemical suppliers to get experimental data that we can use to get highly accurate toxicity prediction
- Leading certifying agencies to certify the toxicity reports we generate
- Toxicity prediction model designers who can host their models (licensing to our customers) for real-time tox-predictions

What does this mean for different industries?

For Pharma, Biochem, Agrochem sectors and chemical suppliers, companies can:

- Weed out high-risk drug targets before investing R&D efforts
- Avoid toxic raw material, minimize the costly late-stage process changes, achieve faster go-to-market
- Ensure product compliance with most of the countries regulations
- Reduce toxic waste generation by up to 90%

For Consumer goods, cosmetics, electronics sectors:

- Trusted formulation toxicity evaluation based on ingredients interactions, amount of chemicals involved, and environmental factors
- Ability to aggregate toxicity involving multiple formulations
- Identify region-specific compliance issues, avoid product's usage specific, and target user group related acute and chronic issues before the product is released

6. Future improvements, other products

Having built the most comprehensive toxicity database in the worldwide market covering most organic and inorganic chemicals,

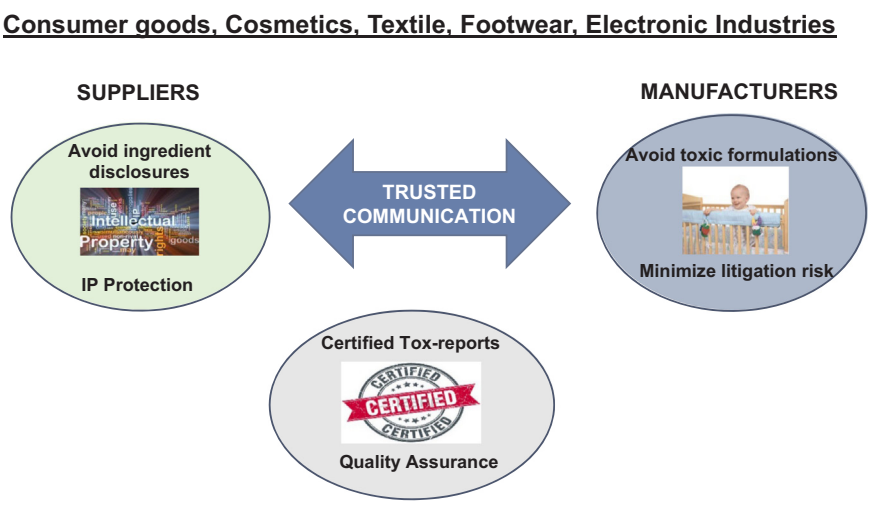


Fig. 4. Benefits Of Using ViridisChem For Toxicity Evaluation Of Formulations.

polymers, petrochemical-related mixtures, etc. as well the integrated information on most regulatory list, toxic chemicals thresholds, we are able to expand our platform to perform toxicity evaluation of materials, nutraceuticals. Some of the future products we are hoping to develop are:

Toxicity evaluation platform for Nutraceuticals, Cosmetics, Drug – interactions

7. Lessons learned, how can we help other startups to succeed?

- One of the biggest challenges we faced is how to prioritize the industries we should focus on. Since chemicals are used in 96% of worldwide products, our software products can be useful within almost all industries. But we want to customize our products for different industries, so that we can provide the most critical information needed by the researchers within those industries.

We decided to initially focus on the Pharmaceutical industry and the education sector to build a robust tool with rich features that can help research departments. We received very valuable feedback that has helped us enrich our product. Our next focus will be the Chemical Suppliers so that we can validate our data with their experimental data and enrich the database. We are also building the Formulation Analyzer that will enable seamless trust and dialog among the suppliers and manufacturers.

- The second biggest hurdle we have experienced is the reach to the investor community in the Silicon Valley, California. Green Chemistry is a new and unknown market for many, and it still has not yet received the wide acceptance it deserves. Also, our solutions cross between the Life-science and Software-AI-SaaS investor interest and finding the investor who can appreciate both verticals and underlying logistics is harder than usual. Additionally, in spite of the active support and encouragement offered by the global community, I feel that getting serious interest from the investor community is more difficult for women entrepreneurs.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.scp.2018.11.005.

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