Chemical Research in Toxicology

pubs.acs.org/crt

ToxWatch

Metabolism and Toxicity of Fluorine Compounds

Jillian L. Kyzer* and Marvin Martens*

Cite This: *Chem. Res. Toxicol.* 2021, 34, 678−680

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Fluorine has many beneficial features and applications but can cause toxicity at high doses. Herein, we describe its chemical properties and benefits to agrochemical design as well as potential metabolic liabilities and exposure assessment *in vivo*.

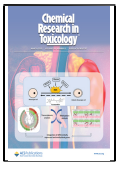
The use of fluorine in drugs and agricultural chemicals has greatly expanded since the first fluoro compound, fludrocortisone, was approved in 1955. In 2018−2019, 45% of small molecule drugs approved by the U.S. Food and Drug Administration and 52% of agricultural chemicals between 2010 and 2017 contained fluorine.[1] Summaries of the key properties underlying the popularity of fluorine, its risks, applications, and exposure assessment *in vivo* were presented at the 2020 American Chemical Society virtual meeting during the Chemical Toxicology Division thematic session "Metabolism and Toxicity of Fluorine Compounds".[2]

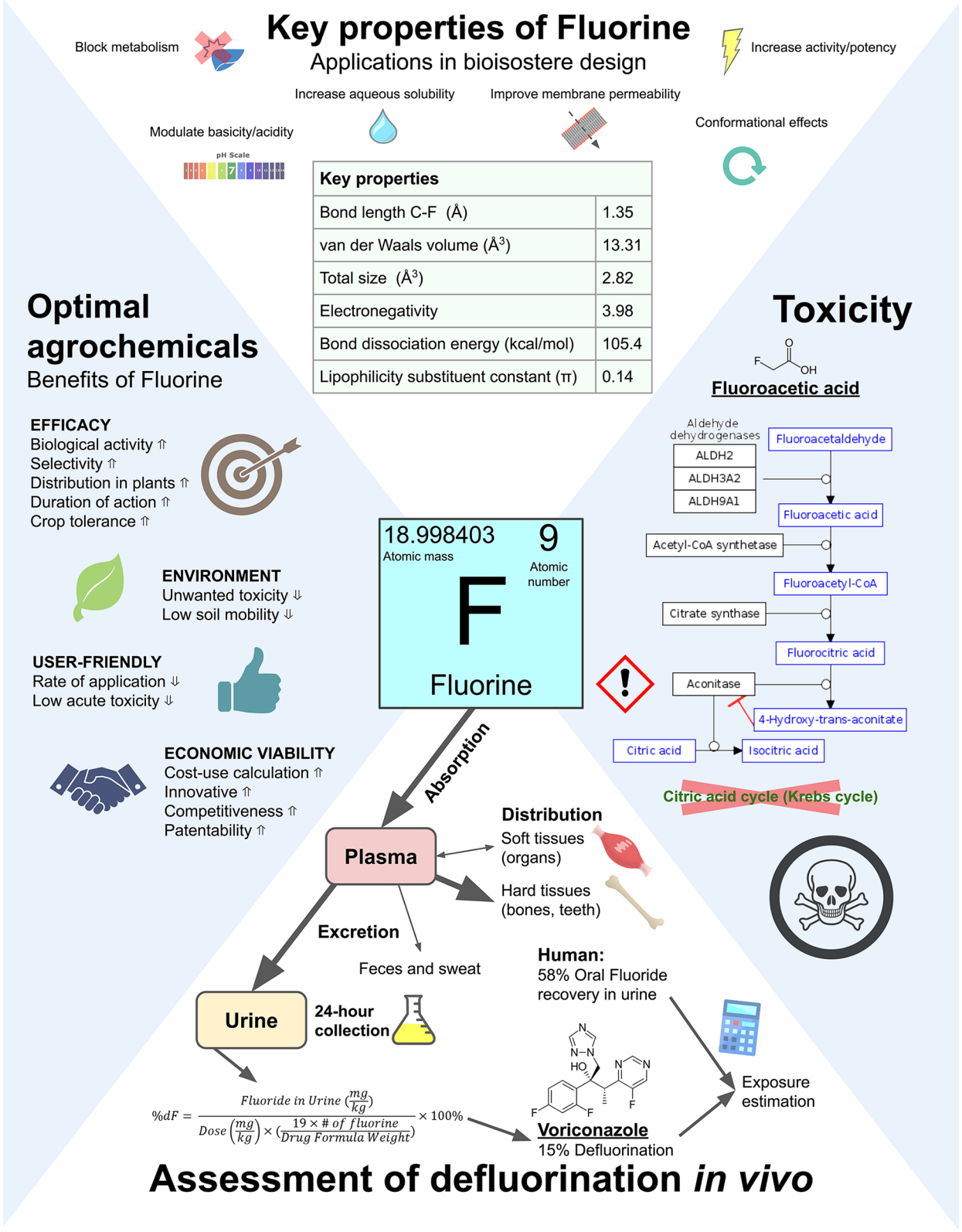
Nicholas Meanwell from Bristol Myers Squibb discussed the relationship between the use fluorine and its intriguing properties.[3] The size of a fluorine atom is similar to that of a hydrogen atom, but the C−F bond length is more similar to that of a carbonyl. Additionally, due to fluorine's electronegativity, the bond is polarized. These properties, combined with the strength of the C−F bond (105.4 kcal/mol), have made fluorine a useful bioisostere for a variety of functional groups including hydrogens, carbonyls, and nitriles. The presence of nearby fluorine can also alter functional group acid dissociation constant (pK_a), reducing the basicity of proximal amines and increasing acidity of acids. The presence of a fluorine atom can also alter conformational structure, as fluorine prefers a gauche relationship with some substituents, providing a stabilization energy in excess of 1 kcal/mol. In a series of dipeptidyl peptidase 4 inhibitors, the presence of a fluorine on a pyrrolidine ring resulted in stabilization of either an *endo* or *exo* conformation, depending on the stereochemistry of the fluorine, markedly affecting potency. Fluorine has been extensively utilized to block metabolism. The methylenedioxy moiety is a common functional group in natural products and some drug molecules, and it is subject to metabolism by cytochrome P450 enzymes that results in the formation of a carbene that binds tightly to the catalytic iron atom and inhibits the enzyme. Difluorination of the methylenedioxy moiety in a series of camptothecin analogs provided metabolic stability and allowed for oral administration. In some cases, fluorination of an *N*-alkyl of an amide has been shown to reduce *N*-dealkylation.

Peter Jeschke (Bayer) presented the application of halogens, such as fluorine, in agrochemical design.[1] On average, insecticides contain 4 halogen atoms per molecule, while fungicides contain 3 halogens and herbicides contain 2.5 halogens. The addition of halogen atoms like fluorine, while occasionally important for efficacy through improved biological activity, selectivity, crop tolerance, and distribution, also has dramatic impacts on soil stability and water solubility, making the agrochemicals more environmentally safe. These aspects, along with the user-friendliness and economic viability, are important factors to consider in the search for the optimal product in crop protection.

Despite the strength of the C−F bond, fluorine can act as a leaving group.[4] While fluoride can be beneficial in small doses, amounts >10 mg/day can be toxic and potentially result in skeletal fluorosis and gastrointestinal side effects in humans. Other fluorinated compounds can also affect human health, as discussed by Benjamin Johnson from Bristol Myers Squibb. One particularly harmful metabolite of some fluorine-containing drugs is fluoroacetic acid (median lethal dose, LD_{50} = 10 mg/kg in humans). Fluoroacetic acid can disrupt the Krebs cycle following reaction with acetyl coenzyme A and entry into the pathway. This metabolic pathway results in the production of 4-hydroxy-*trans*-aconitate which is a reversible but tight-binding inhibitor of aconitase, thus impairing oxidative metabolism. The most common metabolic sources of fluoroacetic acid are fluoroamines and fluoroethers. However, other moieties can result in the production of fluoroacetic acid via less typical routes, such as in the case of an α-fluoroketone, designed as a cysteine protease inhibitor, which was shown to produce high concentrations of fluoroacetic acid; the proposed mechanism of fluoroacetic acid production involves a Baeyer−Villiger reaction with an enzyme-based peroxide. The insertion of an oxygen adjacent to the ketone to produce the acid is facilitated by the electronegativity of the fluorine α- to the ketone. Fluorinated ethers, such as OCF_3, are often used to interfere with the metabolism of an OCH_3 or replace an ethyl group. However, a 2015 Pfizer study revealed that, in general, there was no additional metabolic stability conferred by replacing the

Published: January 29, 2021





methoxy group with a trifluoromethoxy group. One clinical candidate contained a *para*-substituted aminotrifluoroanisole, which can be converted to a quinone imine intermediate and ultimately results in the loss of the OCF_3 group. This leaving group rapidly collapses to form fluorophosgene.

Due to the potential toxicity associated with liberation of fluoride, it is important to have a mechanism in place to determine exposure *in vivo*, which was the focus of the presentation by Qiuwei Xu (Merck).[5] After fluorine is liberated from a fluorine-containing drug through metabolic oxidation, glutathione displacement, or nucleophilic substitution, it is distributed in the body's hard and soft tissues. Whereas uptake by soft tissues reaches steady state, a large fraction is taken up by the bones and teeth. Excretion occurs through feces and sweat, but the majority of fluoride is cleared by the kidneys and ends up in the urine. Thus, screening the urine is the most optimal

https://dx.doi.org/10.1021/acs.chemrestox.0c00439
Chem. Res. Toxicol. 2021, 34, 678−680

measure of total exposure. The researchers dosed humans, rats, beagle dogs, and rhesus monkeys with known doses of sodium fluoride, then determined the percentage of fluoride excreted in the urine. In humans, this value was found to be ∼58% and can be used to back-calculate the total exposure for various fluorinated drugs. For example, prolonged administration of large doses of voriconazole resulted in toxicity, and previous studies showed that defluorination of voriconazole amounts to 15% (defluorination percentage, %dF). Using the risk calculation to estimate the total fluoride exposure in the body, it was determined that 400 mg doses of voriconazole resulted in an estimation of 17.5 mg/day of fluoride exposure.

The use of fluorine in pharmaceuticals and agrochemicals has expanded dramatically since its first use in the 1950s. Its use is often tied to improved metabolic stability, selectivity, and solubility, which has been demonstrated for a variety of products. However, fluorinated compounds are not immune to metabolism and liberation of fluoride or low molecular weight fluorinated molecules from fluorine-containing drugs, and candidates must be monitored to avoid potentially lethal toxicity.

AUTHOR INFORMATION

Corresponding Authors

Jillian L. Kyzer − *School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53705, United States*; Email: kyzer@wisc.edu

Marvin Martens − *Department of Bioinformatics-BiGCaT, NUTRIM, Maastricht University, Maastricht 6200 MD, The Netherlands*; Email: marvin.martens@maastrichtuniversity.nl

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrestox.0c00439

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Funding was provided by NIH 1R13ES032309-01 for the authors' ACS meeting registrations.

REFERENCES

(1) Jeschke, P. (2017) Latest generation of halogen-containing pesticides. *Pest Manag. Sci. 73*, 1053−1066.

(2) (2020) Proceedings from the *American Chemical Society 2020 Fall National Meeting*, Virtual Meeting, August 17−20, 2020, ACS: Washington, DC.

(3) Meanwell, N. A. (2018) Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem. 61*, 5822−5880.

(4) Johnson, B. M., Shu, Y.-Z., Zhuo, X., and Meanwell, N. A. (2020) Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. *J. Med. Chem. 63*, 6315−6386.

(5) Villa, A., Anabalon, M., Zohouri, V., Maguire, A., Franco, A. M., and Rugg-Gunn, A. (2010) Relationships between fluoride intake, urinary fluoride excretion and fluoride retention in children and adults: an analysis of available data. *Caries Res. 44*, 60−68.

https://dx.doi.org/10.1021/acs.chemrestox.0c00439
Chem. Res. Toxicol. 2021, 34, 678−680