PFAS REACH Annex XV Restriction Report 1ST Public Consultation (22 March – 25 September 2023)

Exclusion of Trifluoroacetic Acid from the PFAS Proposal for a Restriction

General Comments:

Sinochem Lantian Fluoro Materials Co., Ltd. is a company mainly engaged in fluorinated polymers and fluorinated fine chemicals. Fluorinated fine chemicals include 1,1,1-trichloro-2,2,2-trifluoroethane, trifluoroacetyl chloride, trifluoroacetic acid (TFA), ethyl trifluoroacetate and other related derivative products of TFA. The production of TFA is globally leading.

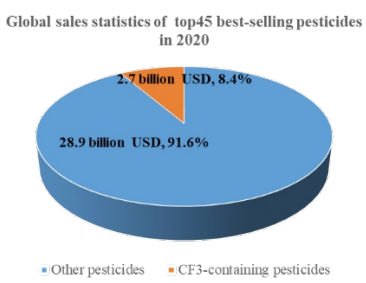
Our company supports the EU's efforts to reduce the risk of hazardous substances and believes it is necessary to reduce the use of PFAS. But we consider that TFA should be excluded from the PFAS proposal, because of the irreplaceable role of TFA in the production process of pharmaceutical and pesticides.

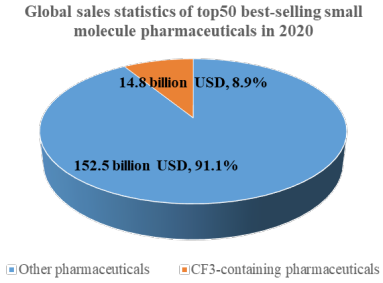
There are two reasons to support this view. Firstly, the Dossier Submitter of PFAS Proposal from five national authorities consider that the derogation covers all preceding steps that are necessary to produce the product, including pharmaceuticals and pesticides that complied with relevant EU regulations. But there is no specific definition of necessary production. As all know, CF_3-containing pharmaceuticals and pesticides play a critical role in global market. Currently, the main raw materials for large-scale production of CF_3-containing aliphatic and heteroaromatic products are TFA and related derivatives, which are difficult to replace with other raw materials or synthesis methods. In addition, TFA could also be used as reaction solvent, analytical reagent, protective reagent, and deprotective reagent, which are widely used in production of pharmaceuticals and pesticides. Therefore, TFA should be considered as a critical part of necessary production and excluded from the production of pharmaceuticals and pesticides. Secondly, although the CF_3-containing pharmaceuticals and pesticides are excluded from the proposal, the fact of their degradation products contain TFA is obviously existence. If TFA cannot be excluded

from the proposal, it will have a serious impact on the development of new CF_3-containing products and even the whole industry of pharmaceuticals and pesticides.

1. TFA should be considered as a critical part of necessary production and excluded from the production of pharmaceuticals and pesticides.

CF_3-containing pharmaceuticals and pesticides play a critical role in human health and food safety. According to statistical data from Jon T. Njardarson group[1][i], there were five CF_3-containing products with a total sale of 14.8 billion USD and a proportion of 8.9%, among the top50 small molecule pharmaceuticals by retail sales in 2020, including enzalutamide, sitagliptin, sitagliptin/metformin combination, teriflunomide, and nilotinib. According to statistical data from Phillips McDougall[2][ii], there were also five CF_3-containing products with a total sale of 2.7 billion USD and a proportion of 8.4%, among the top45 pesticides (fungicides, insecticides, herbicides) by sales in 2020, including trifloxystrobin, picoxystrobin, cyhalothrin, fipronil, and bifenthrin.



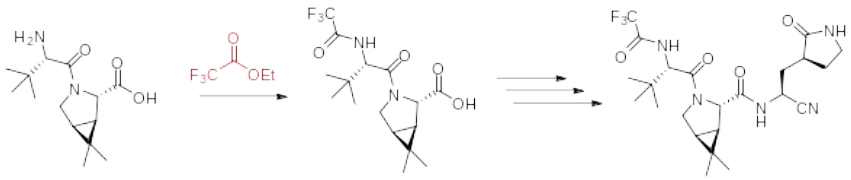


In the production process of pharmaceuticals and pesticides, there are three main methods for introducing trifluoromethyl into molecules. The first one is chlorination and then fluorination of methyl on molecules. This method has limitations such as use of toxic gases (Cl_2 and HF), high requirements for equipment, and low chemical selectivity. The second method is using trifluoromethylation reagents such as halogenated trifluoromethane, $TMSCF_3$, Togni reagent, Langlois reagent, and Umemoto reagent. This method can regioselectively introduce trifluoromethyl into molecular, but there are limitations such as expensive reagents, poor atomic economy, harsh reaction conditions, and difficulty in large-scale production. The third method is

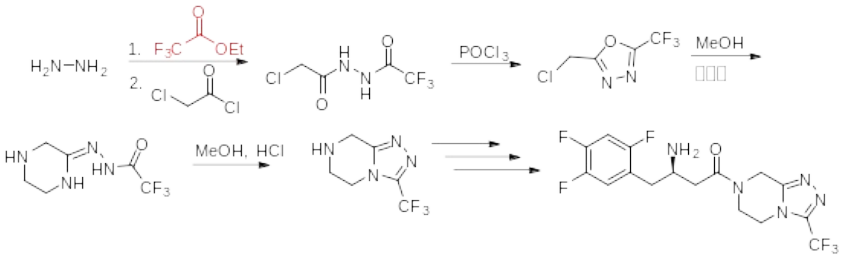
using TFA and related derivatives as raw materials to construct target molecules through functional group conversion or carbon-carbon bond formation. This method has the advantages of good selectivity, mild conditions, high yield, and low cost. It is currently the main method for large-scale production of CF_3-containing aliphatic and heteroaromatic products, which is difficult to be replaced by other raw materials or synthesis methods. According to statistics, the global consumption of TFA and related derivatives reached 40000 tons in 2022 and maintained a strong growth trend, with an expected average annual growth of 1500 tons/year. There are several typical examples as follows:

1.1 Pharmaceutical production

Nirmatrelvir is one of active ingredients in the anti COVID-19 drug Paxlovid, which was approve by EMA in 2022[3]iii. In the same year, the global sale of Paxlovid is 18.9 billion USD, ranking 1st in global best-selling small molecule pharmaceuticals. The patented synthesis route of nirmatrelvir is to first construct a trifluoroacetamide group using ethyl trifluoroacetate as the raw material, and then synthesize the target molecule through multi-step reactions[4]iv. There is no industrialized alternative route so far.

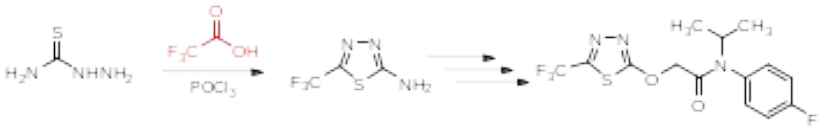


Sitagliptin is a commonly used diabetes drug authorized by HMA[5]v. In 2022, the global sale of sitagliptin is 2.8 billion USD, ranking 23rd in global best-selling small molecule pharmaceuticals. The patented synthesis route of sitagliptin is to first construct trifluoromethyl oxadiazole intermediate using ethyl trifluoroacetate as raw material, and then synthesize the target molecule through multi-step reactions[6]vi. There is no industrialized alternative route so far.

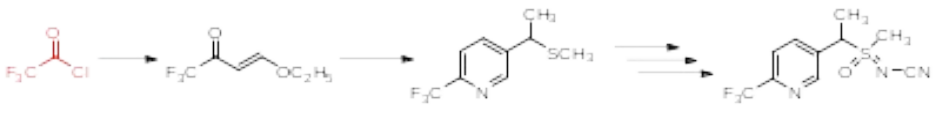


1.2 Pesticide production

Flufenacet is a herbicide developed by Bayer and authorized by the European Commission[7][vii]. The global sale is 0.25 billion USD in 2019. Flufenacet is widely used in many countries all over the world, including the EU. The patented synthesis route of flufenacet is to first construct trifluoromethyl thiadiazole intermediate using TFA as raw material, and then synthesize the target molecule through multi-step reactions[8][viii]. There is no industrialized alternative route so far.



Sulfoxaflor is a neonicotinoid insecticide developed by Corteva and authorized by the European Union. The global sale is 0.19 billion USD in 2019. Sulfoxaflor has become an alternative product of traditional neonicotinoid insecticides due to low bee toxicity. The patented synthesis route of sulfoxaflor is to first construct trifluoromethyl pyridine intermediate using trifluoroacetyl chloride as raw material, and then synthesize the target molecule through multi-step reactions[9][ix]. There is no industrialized alternative route so far.



1.3 Other application

In the production process of pharmaceuticals and pesticides, TFA could not only be used as the raw material, but also as reaction solvent, analytical reagent (such as

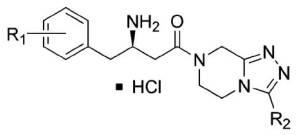
HPLC mobile phase), deprotection reagent for protective groups, and protective reagent for amino groups. It is widely used in the synthesis of complex molecules such as amino acids, peptides, and steroids.

1.2 Due to the serious impact on the development of new CF_3-containing products and even the whole industry of pharmaceuticals and pesticides, TFA should be excluded from the proposal.

Trifluoromethyl functional group is widely used in the design and development of pharmaceuticals and pesticides due to its strong electron withdrawing ability, which can change the charge distribution and configuration of molecules, thereby affecting their physical and chemical properties and enhancing biological activity. In the field of drug development, trifluoromethyl is often used to improve the cell membrane permeability and pharmacokinetic properties of drugs, such as increasing oral bioavailability and reducing liver metabolism. The interaction between drug molecule and target enzyme could be enhanced, while the activity and selectivity of drug improved by introducing trifluoromethyl[10].2]

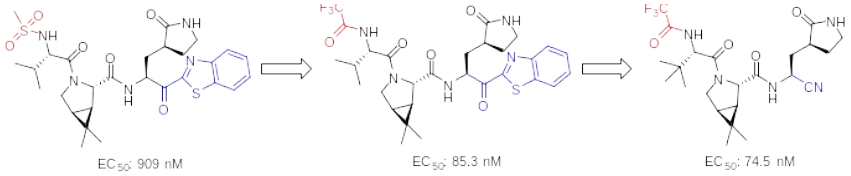
For example, during the discovery of sitagliptin, when the substituent R is trifluoromethyl, its activity is significantly higher than H, ethyl, perfluoroethyl and other substituents[11.T]

able 6 Inhibitory activity of sitagliptin derivatives on target enzymes



compd	R1	R2	DPP-IV IC_{50} (nM)	QPP (nM)	DPP8 (nM)	DPP9 (nM)
22	3,4-di-F	H	455	>10000	38000	>100000
23	3,4-di-F	Et	231	64000	45000	>100000
24	3,4-di-F	CF_3	128	98000	46000	>100000
25	2,5-di-F	CF_3	27	>100000	69000	>100000
1	2,4,5-tri-F	CF_3	18	>100000	48000	>100000
26	2,4,5-tri-F	H	68	>10000	72000	>100000
27	2,4,5-tri-F	CF_2CF3	71	78000	80000	>100000
28	2,5-di-F	CH_2CF_3	103	>100000	35000	>100000

Another example is the discovery of nirmatrelvir. The antiviral activity has been significantly improved by 10 times by the replacement of the methanesulfonyl with trifluoroacetyl on the amino group[12.]



In the field of pesticidedevelopment, trifluoromethyl is often used as a bioisostere of halogen, cyano, and short chain alkyl groups in the molecular design to enhance the activity and persistence[13if]. For example, the fungicide picoxystrobin is optimized based on the structure of kresoxim-methyl. By replacing phenyl with trifluoromethyl pyridine group, the nternal absorption, luidity, and metabolic stability of pesticides could be improved, thereby showing better activity against bacteria[14.pKPffI x×√ ×√××3s]

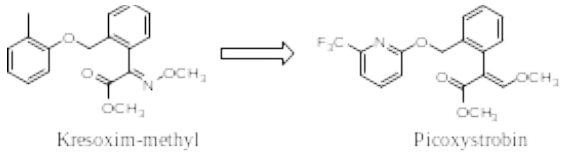
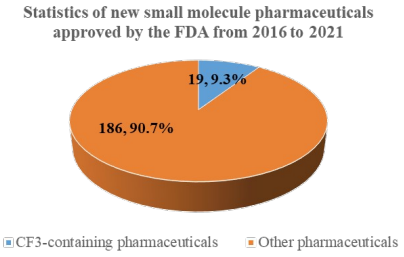


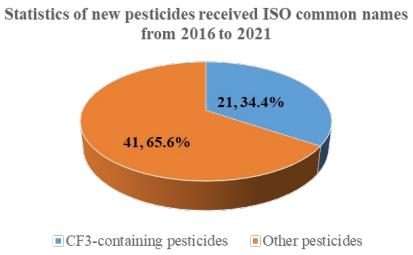
Table 7 Redistribution roperties of kresoxim-methyl and picoxystrobin

	resoxim-methyl	icoxystrobin
Fluidity in leaf	low	medium
Metabolic stability in lea	low	stable
Transfer luidity	low	medium
nternal absorption inylem		
Internal absorption in newleaf		
Fluidity in phloem		

Due to the unique properties of trifluoromethyl, CF-containing pharmaceuticaland pesticides have become an important direction for new product development. According to statistical data from FDA[153], there are 19 new CF-containing products with a proportion of 9.3%, among 205 new small molecule pharmaceuticals approved by the FDA from 2016 to 2021. According to statistical data from the British Crop Protection Council (BCPC)[163333 . O, d3 P., there are 21 new CF-containing products with a proportion of 34.4%, among the 61 new pesticides that received ISO common names from 2016 to 2021. Moreover, there are still many new CF-containing pharmaceuticals and pesticides in the product development pipeline, while companies have invested a lot of manpower and resources in the early stage.

Although the CF-containing pharmaceuticals and pesticides are excluded from the proposal, the fact of their degradation products contain TFA is obviously existence. If TFA cannot be excluded from the proposal, it will bring great risks to the approval of new products in the EU, thereby having a serious impact on the development of new CF-containing products and even the whole industry of pharmaceuticals and pesticides.





3. Conclusion

TFAcould be wildly used as raw material, reaction solvent, analytical reagent, deprotection reagent, and protection reagentIt has played an irreplaceable role in the production process of pharmaceutical and pesticides. n the other sideue to its great contributions in ensuring human health and food security, CF-containing pharmaceuticals and pesticides an important direction for new product development with good application prospects. If TFAis treatedas PFSA substance, it will have a serious impact onthe development of new CF3-containing products and even the whole industry of pharmaceuticals and pesticides. Therefore, we hope to distinguish TFA from other PFAS substance and exclude it fromroposal

References:

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