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Potential degradation of methine (-CH<) compounds

Contents

Summary

In the Annex XV report "Proposal for a restriction of Per- and polyfluorinated substances (PFAS)" several structural exclusions based on evidence from scientific literature are formulated concerning substances which can mineralize under decomposition of the perfluoro moiety: "A substance that only contains the following structural elements is excluded from the scope of the restriction:CF_3-X or X-CF_2-X', where X = -OR or -NRR' and X' = methyl (-CH_3), methylene (-CH_2-), an aromatic group, a carbonyl group (-C(O)-), -OR'', -SR'' or –NR''R'''; and where R/R'/R''/R''' is a hydrogen (-H), methyl (-CH_3), methylene (-CH_2-), an aromatic group or a carbonyl group (-C(O)-).)."

The authorities noted that the restriction proposal is not entirely based on sufficient comprehensive data. Therefore, further input from the industry is necessary to fill knowledge data gaps. According to the OECD definition a large variety of molecules are considered to be PFAS and, thus, are in scope of the EU restriction proposal. Although several structural elements are excluded, the restriction as suggested has a massive impact on many sectors, but industry has only a period of six months to comment on uses and degradation pathways. Depending on the complexity of the supply chain, the consideration of all use conditions is difficult within the consultation period but the generation of scientific data on potential degradation pathways is impossible. We are facing a variety of structures having a variety of metabolites which would need to be analyzed by using a suitable degradation test and development of new analytical methods to provide scientific evidence. Therefore, we screened literature for missing degradation pathways of further molecules which should, in our opinion, also be excluded from the PFAS restriction.

The set of groups which are already excluded from the EU PFAS restriction comprises for example methyl, methylene and aromatic moieties, but does not contain the methine group (-CH<). From a chemist's point of view, aromatic groups are generally more stable compared to methine groups. Thus, a CF_2-O- group adjacent to a methine group should mineralize more readily compared to a CF_2-O- group adjacent to aromatic groups. We screened literature for potential degradation pathways of cyclohexanes and branched alkyl chains to provide a basis for the exclusion of methine groups from the proposed PFAS restriction. Based on examples found in literature, the degradation of methine groups adjacent to the -CF_2-O- moiety can lead to carbonyl compounds which are already considered for an exclusion because of their ability to fully degrade to CO_2, H_2O and HF, leaving no persistent fluorinated organic metabolites.

Degradation pathways known from scientific literature

The methine group adjacent to the -CF_2-O- group was chosen as target to screen literature. Degradation usually involves oxidation and degradation steps and we assumed a degradation cascade should lead to -C(O)-CF_2-O- compounds which are excluded from the PFAS restriction, because of their ability to fully degrade to CO_2, H_2O and HF was indicated in the restriction proposal.

Degradation pathway of alkanes[1, 2]

In marine environment under aerobic conditions, alkanes are known to be oxidized at the terminal carbon atoms and at subterminal carbon atoms, whereas the oxidation at the terminal carbon atom is favored (figure 1). In an oxidation cascade, the alcohol is oxidized to the aldehyde and finally to the carboxylic acid.[1, 2]

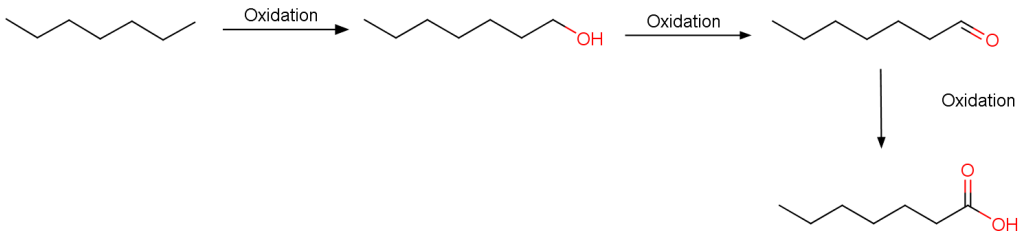

Figure 1: Fatty acid degradation: Mechanism of terminal oxidation.[1, 2]

These carboxylic acids are known to undergo β-oxidation as further degradation pathway.[1,2] Figure 2 describes the pathway of the enzymatic β-oxidation. In step a) the acyl-CoA-synthase binds to the carboxylic acid. In step b) the enzyme acyl-CoA-dehydrogenase forms a double bond in β position. The double bond is hydrated by the 2,3-enoyl-CoA-hydratase in step c) to the alcohol and is further oxidized to the ketone by 3-hydroxyacyl-CoA dehydrogenase in step d). In the final step e) of the first cycle, an acyl is cleaved by the 3-oxoacyl-CoA-thiolase.

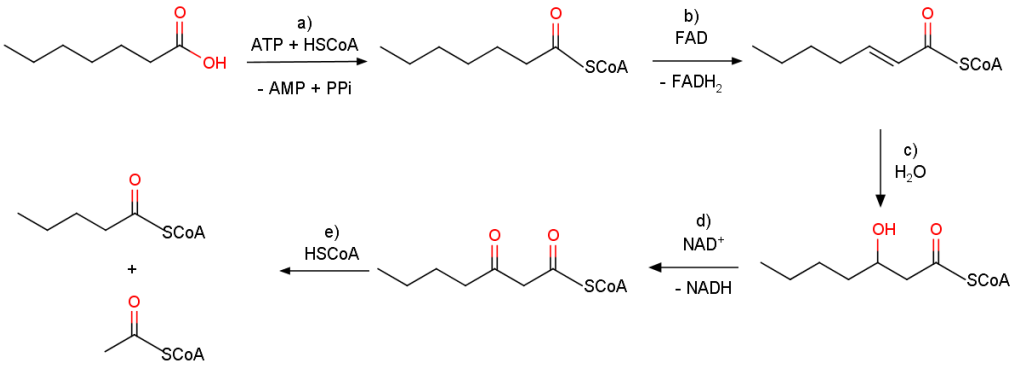

Figure 2: Fatty acid degradation: β-oxidation and acetyl cleavage.[1, 2]

Degradation of branched alkanes[3]

The degradation of alkylbenzensulfonate surfactants in sewage treatments plants has been investigated and the involved mechanism was postulated (figure 3).[3] In step a), a branched carboxylic acid reacts with acyl-CoA-synthase. In step b) the enzyme acyl-CoA-dehydrogenase forms a double bond in β position which is hydrolyzed in step c). In step d) the keto-acid lyase cuts the molecule to the ketone and the carboxylic acid. The ketone is then further degraded to the succinate in a multistep degradation mechanism (not shown here).

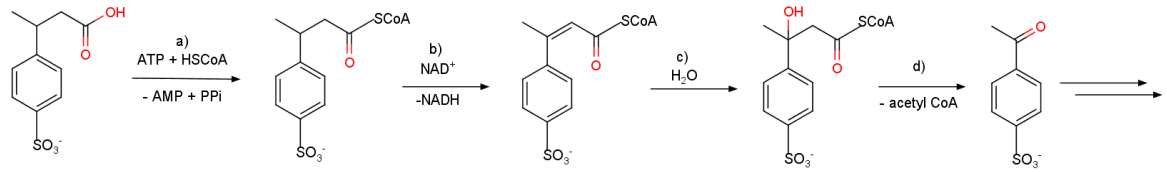

Figure 3: Degradation of alkylbenzensulfonate surfactants.[3]

Degradation of cycloalkanes[1, 2]

In the group of cycloalkanes, especially cyclohexanes are well studied and known to degrade in marine environment via oxidation to cyclohexanol catalyzed by cyclohexane monooxygenase in step a) (Figure 4). In step b) cyclohexanol is oxidized induced by the cyclohexanol dehydrogenase to cyclohexanone. The cyclohexanone monooxygenase transfers this molecule together with the coenzyme NADH to the ε-caprolacton in step c) which is subsequently hydrolyzed in step d) and further oxidized to a dicarboxylic acid in step e). The dicarboxylic acid is capable of β-oxidation to acetyl-CoA analogue as shown in figure 2.

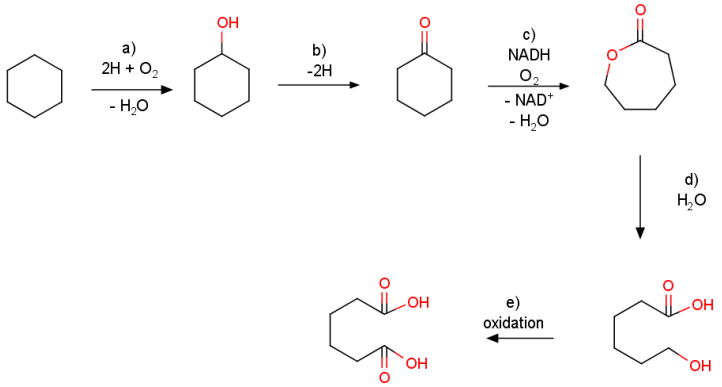

Figure 4: Degradation mechanism of cyclohexane.[1, 2]

Transfer of literature-known degradation pathways to PFAS molecules

Potential degradation pathway of branched alkyls in α-position to perfluoro -CF_2-O-groups

For branched alkyl chains having a methine group in α-position to perfluoro -CF_2-O- groups, we assume that β-oxidation (analogue to figure 2) is also a viable decomposition pathway after the initial oxidation of the terminal carbon (analogue to figure 1). In the model compound shown in figure 5, one of the branches should be oxidized at the terminal carbon atom to a carboxylic acid (see step a). In step b) the compound can be oxidized under double bond formation in β-position. The double bond should be hydrated in step c). The methine carbon atom in α-position to the -CF_2-O- group cannot be oxidized to the corresponding ketone via the β-oxidation mechanism, but alternative degradation pathways are possible and described in literature. One potential pathway after the oxidation to the alcohol can be acyl cleavage where the compound is split to the ketone and the carboxylic acid (step d). The ketone compound has the structural X-CF_2-X' motif, which is excluded from the EU PFAS restriction proposal, as this compound can further mineralize. The degradation pathway of the model compound to the ketone seems to be possible. A simulation using the EAWAG-BBD Pathway Prediction System (PPS) led to similar degradation steps and similar final compounds. The PPS predicts plausible pathways for microbial degradation of chemical compounds and uses biotransformation rules based on reactions found in the EAWAG-BBD database or in the scientific literature.[4]

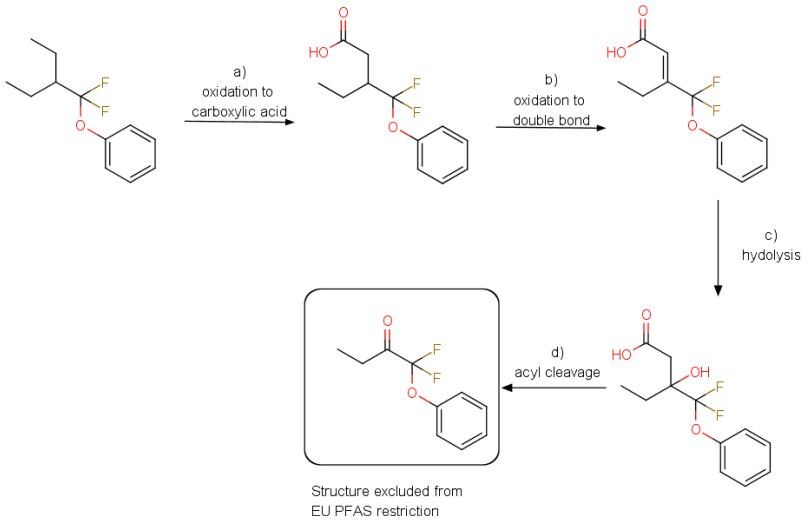

Figure 5: Potential degradation pathway of the model compound (2-ethyl-1,1-difluorobutoxy)benzene in analogy to the β-oxidation mechanism with subsequent acyl cleavage.

Potential degradation of substituted alkyl cyclohexanes

In the hypothetical example as shown in figure 6, the degradation could start in step a) with the terminal oxidation and the subsequent β-oxidation of the alkyl chain to the carboxylic cyclohexane derivative. The cyclohexane moiety is rotationally symmetric, so that there are two chemically different carbon atoms which can be oxidized to the alcohol and subsequently to the ketone in analogy to figure 4. The ketone should then be oxidized to the ε-caprolactone (steps b) and g). In step c) the caprolactone is hydrolyzed and oxidized to the tri carboxylic acid, which can be shortened by β-oxidation (step d). The methine carbon atom should be oxidized to the alcohol (step e) and should be split in step f) to a compound which is excluded from the EU PFAS restriction proposal. After hydrolysis and oxidation (step h), the second caprolactone can form a carbonyl compound which is excluded from the draft EU PFAS restriction proposal as well. The potential degradation pathway to the ketone seems to be possible. A simulation using the EAWAG-BBD Pathway Prediction System (PPS) led to similar degradation steps and similar final compounds.[4]

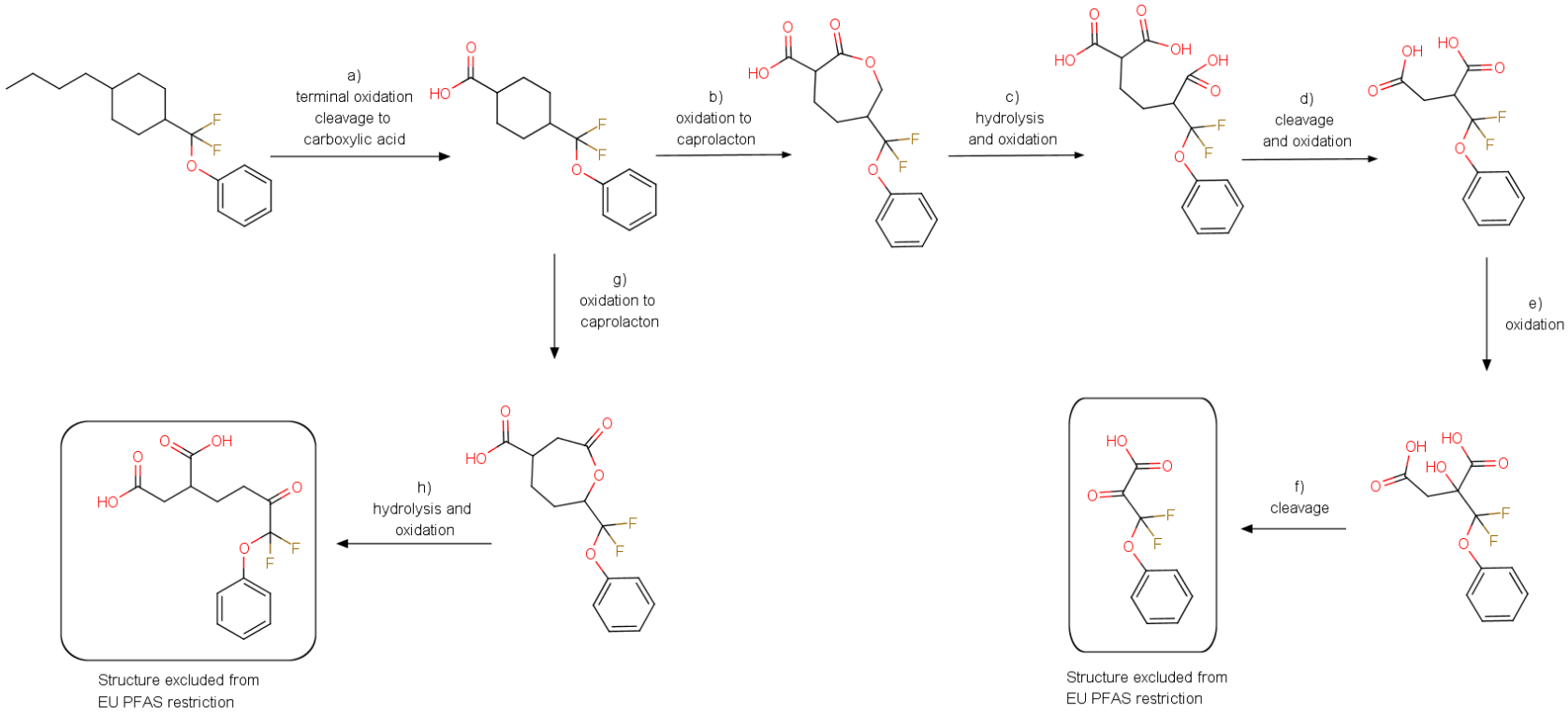

Figure 6: One potential degradation pathway of an alkyl cyclohexane moiety.

Conclusion

Although the described mechanisms are hypothetical with model compounds, literature to each of the potential degradation steps with a fitting substructure is available and the EAWAG-BBD Pathway Prediction System supports the proposed mechanism. Therefore, we expect that the model compounds are able to fully mineralize to CO_2, H_2O and HF, leaving no persistent fluorinated organic metabolites. Hence, further structural motifs should additionally be excluded from the proposed PFAS restriction.

In comment no 4418 Merck Electronics has shown further fluorosurfactant compounds which are not fulfilling the exclusion criteria, but are able to fully mineralize to CO_2, H_2O and HF. Based on the use of these fluorosurfactants, an environmental release is possible. Therefore, molecules were designed with potential degradability and the degradation pathway was accurately investigated.

However, higher tier studies on environmental metabolism/degradation, e.g., in soil, freshwater, are not available for low tonnage chemicals or intermediates. Screening results at hand for readily biodegradability are not suitable to clarify their mineralization potential.

Due to the short timeline to comment on the restriction proposal, it is not possible to complete higher tier studies to generate data elucidating the whole degradation pathway for substances in scope of the EU PFAS restriction. Depending on the complexity of the molecule, the expected degradation cascade is quite complex and the development of the analytical methods to determine the presented isomers is complex as well.

We believe, the exclusion criteria for the PFAS definition as presented in the Annex XV report "Proposal for a restriction of Per- and polyfluorinated substances (PFAS)" are not exhaustive. We contributed by literature screening and in our opinion X' = -CH< (methine) adjacent to a -CF_2-O- group should additionally be excluded from the proposed PFAS restriction.

There might be also other PFAS structures which are able to fully mineralize to CO_2, H_2O and HF. It is not possible to prove this ability within the given time of the consultation sufficiently. So, a general exemption for PFAS substances based on sound prove that they fully mineralize should be considered as well.

References

[1] Reineke, W., Schlömann, M., Umweltmikrobiologie, 3rd edition, Springer Spektrum, 2020, 173-185.

[2] Harayama, Shigeaki & Kishira, H & Kasai, Yuki & Syutsubo, Kazuaki. (1999). Harayama S, Harayama S, Kishira H, Kasai Y, Shutsubo K.. Petroleum biodegradation in marine environments. J Mol Microbiol Biotechnol 1: 63-70. Journal of molecular microbiology and biotechnology. 1. 63-70.

[3] Schleheck D, von Netzer F, Fleischmann T, Rentsch D, Huhn T, Cook AM, Kohler HP. The missing link in linear alkylbenzenesulfonate surfactant degradation: 4-sulfoacetophenone as a transient intermediate in the degradation of 3-(4-sulfophenyl)butyrate by Comamonas testosteroni KF-1. Appl Environ Microbiol. 2010 Jan;76(1):196-202. doi: 10.1128/AEM.02181-09. Epub 2009 Nov 13. PMID: 19915037; PMCID: PMC2798632.

[4] http://eawag-bbd.ethz.ch/predict/

Appendix

Degradation pathways as calculated using EAWAG-BBD Pathway Prediction System

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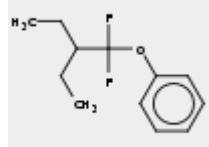

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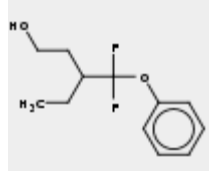

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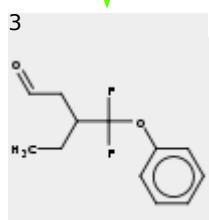

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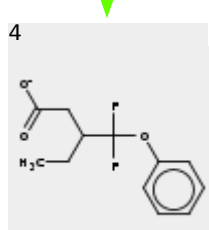

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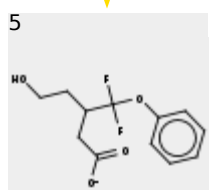

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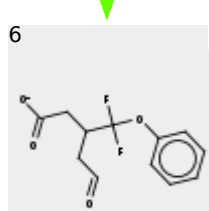

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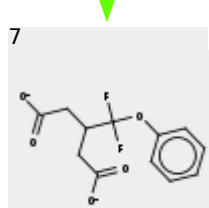

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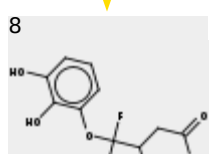

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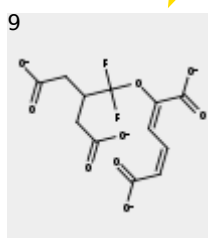

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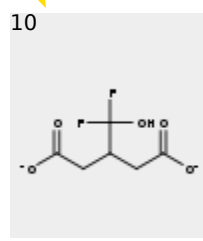

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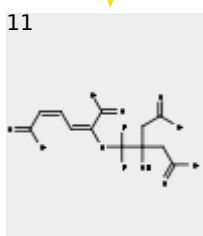

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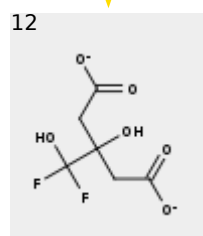

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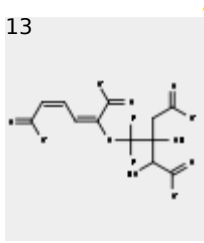

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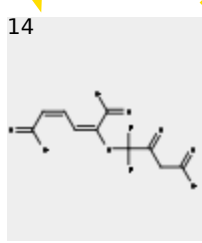

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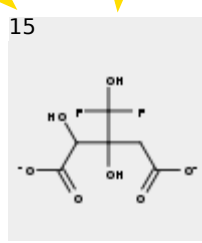

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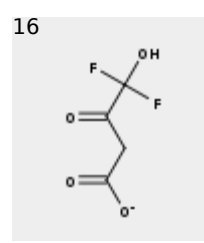

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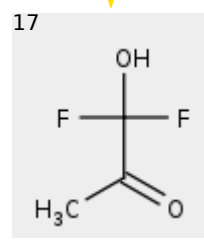

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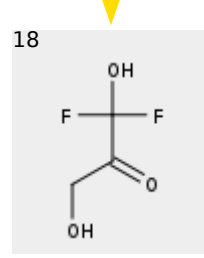

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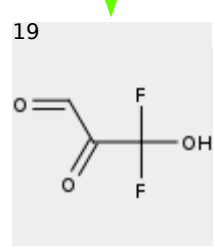

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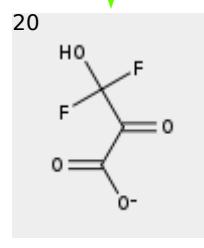

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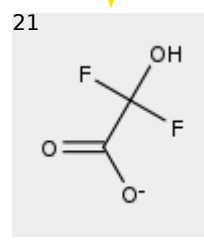

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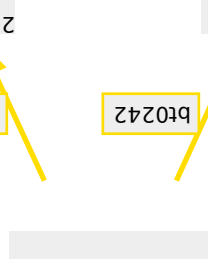

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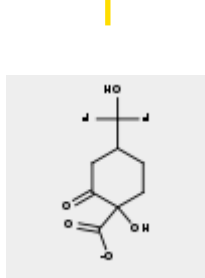

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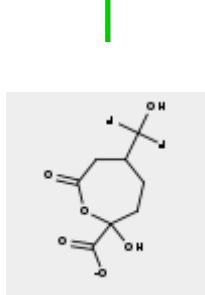

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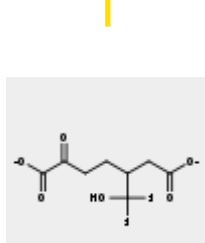

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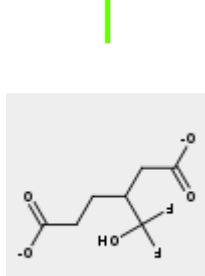

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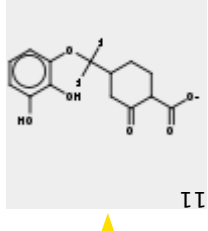

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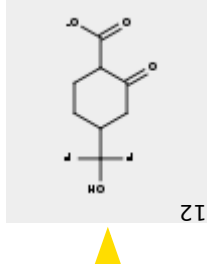

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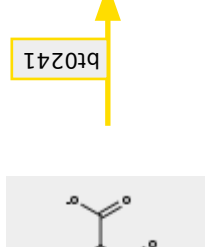

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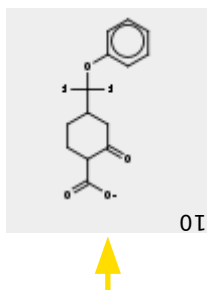

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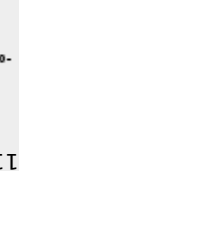

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