Designing Safer Chemicals: Environmental Attributes in Chemical Design

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Green Chemistry and Chemical Design

- Design of the molecule is the earliest phase in the life cycle of commercial chemicals
- Green chemistry principles are central to chemical design
  - Principle #4: Chemical products should be designed to effect their desired function while minimizing their toxicity
  - Principle #10: Chemical products should be designed so that at the end of their function they break down into innocuous degradation products

http://www.epa.gov/greenchemistry/pubs/principles.html

This Presentation, Part I
Focus on Biodegradability

- Use case studies to show how molecular structure can be used to design small molecules for biodegradability
- The case studies are real-world examples from high-volume commercial chemicals
  - Alkylbenzenesulfonate surfactants; fabric softeners; functional fluids (hydraulic fluids, transformer oils, etc.); chelating agents; alkylphenol ethoxylates; gasoline oxygenates
- Highlight challenges of safe design in a world of competing objectives

This Presentation, Part II

Include Other Environmental Attributes

- Extend musk fragrances case study
  - Full structural range of synthetic musks
  - Include target substances as well as established commercial products
  - Touch all bases of the PBT paradigm: include aquatic toxicity and bioaccumulation in addition to biodeg
- Show how environmental attributes might be included in screening prior to development or manufacture
- Show how existing predictive tools and knowledge can be used in this screening
- Seek a more holistic perspective

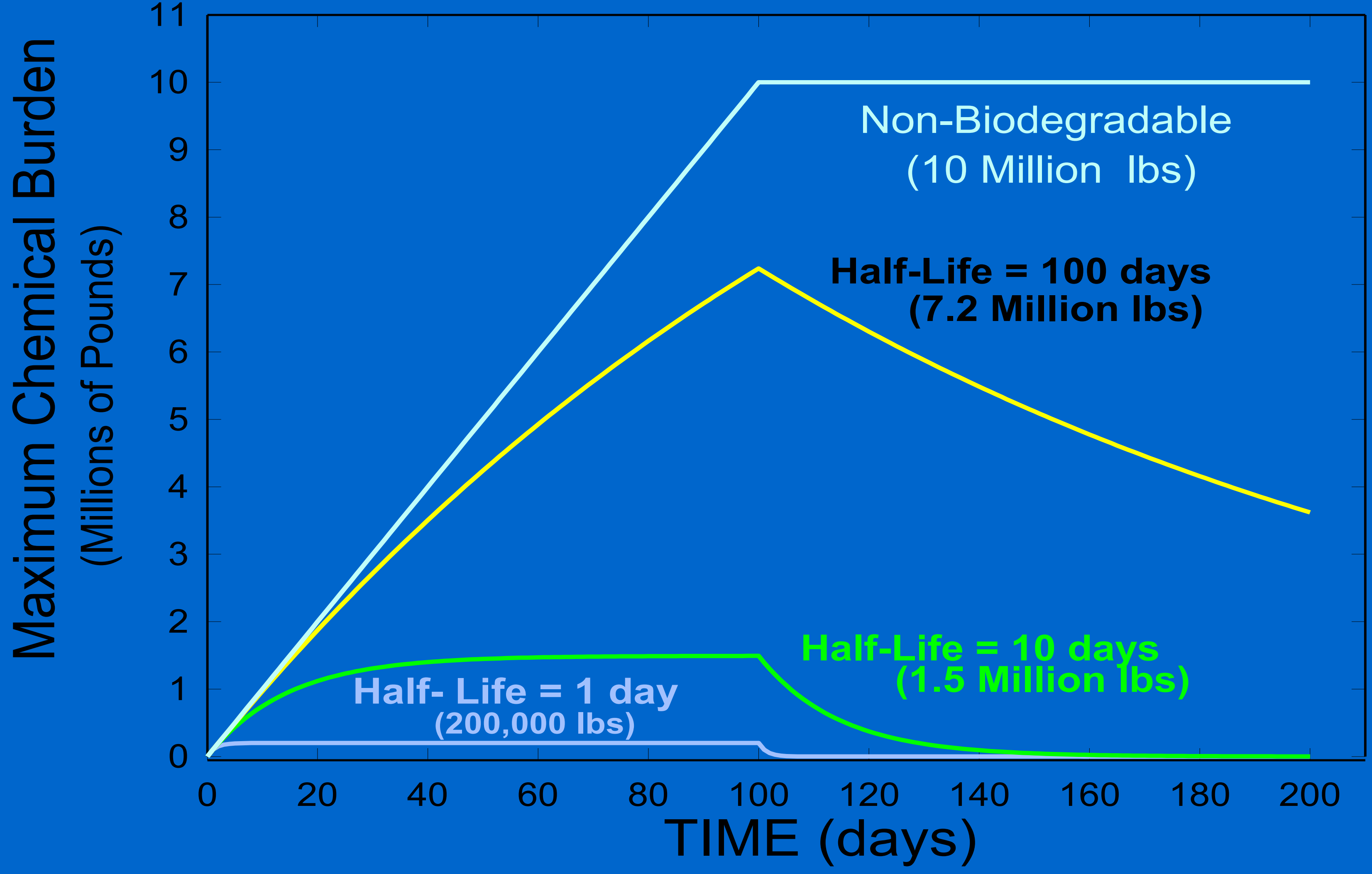
Why Be Biodegradable?

(credit here to Tom Federle, now retired from Procter & Gamble)

- Biodegradability is fundamental in chemical design for many types of substances because
  - Persistent chemicals remain available to exert toxicity. Effects are not always predictable
  - "Source prevention" is not always possible: waste treatment may be critical to control of emissions, and chemicals that break down better reduce risk
- Why should a material be ultimately biodegradable?
  - No additional safety issues relating to persistent metabolites
  - It's an expectation of consumer groups, environmental groups, the media and the technical community

Maximum Chemical Burden to the Environment

Input = 100,000 lbs/day for 100 days then Discontinued



Factors Affecting Biodegradation

- Environmental conditions
  - Local biology
  - Physical/chemical conditions: temperature, pH, etc.
- Inherent properties of the chemical
  - Molecular structure
  - Physical and chemical properties: water solubility, vapor pressure, etc.

List 1
Possible reasons for resistance of a substance to microbial degradation

Environment

- ▶ Appropriate microorganisms don't exist or not present in the environment
- ▶ There are inadequate nutrients for the microbial population
- ▶ Temperature, pH or pO_2 too low or too high; ionic conditions are unsuitable
- ▶ Concentration of substrate too high (toxic) or too low
- ▶ Substrate adsorbed or covalently attached to clays, humus, etc., or physically inaccessible
- ▶ Substrate not accessible to attack because it is too large and/or insoluble

↓

Molecule

- ▶ The substrate
  - — is not transported into the cell
  - — is not a substrate for the available enzymes
  - — is not an inducer for appropriate enzymes or transport systems
  - — does not give rise to products that can integrate into metabolism
  - — is converted into products that are toxic or interfere with metabolism

Molecular Structure and Biodegradability

- The relationship between molecular structure and biodegradability of discrete organics is understood well enough to be applied in molecular design
- Biodegradability is associated with specific structural features (e.g. functional groups), size (molecular mass), water solubility
- Rules of thumb exist. They are not infallible but don't need to be

The Idiot's Guide to Biodegradability:

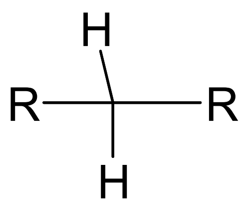
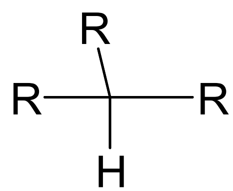
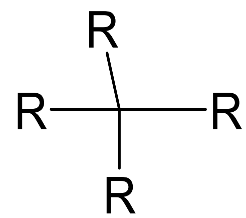
Some positive and negative factors related to molecular structure and properties

negative	**positive**
high molecular weight branching-especially (but not only) quaternary C; also tertiary amine (?) halogens, especially if ≥3 in a small molecule nitrogen heterocycles (e.g. pyridine ring)	low molecular weight linear alkyl chains if not too large hydrolyzable groups (e.g. esters) oxygen (OH, =O, COOH; usually not ether) in molecule

Relationship Between Structure and Biodegradability

More Biodegradable (Less Persistent)	**Less Biodegradable (More Persistent)**

Branching

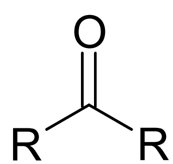
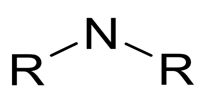
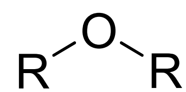
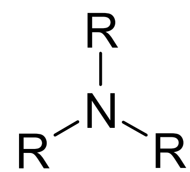
Aliphatic functional groups

$R{-}CH_2OH$

$R{-}CO_2H$

$R{-}NH_2$

R-CHO

Aromatic functional groups (benzene, naphthalene, pyridine rings)

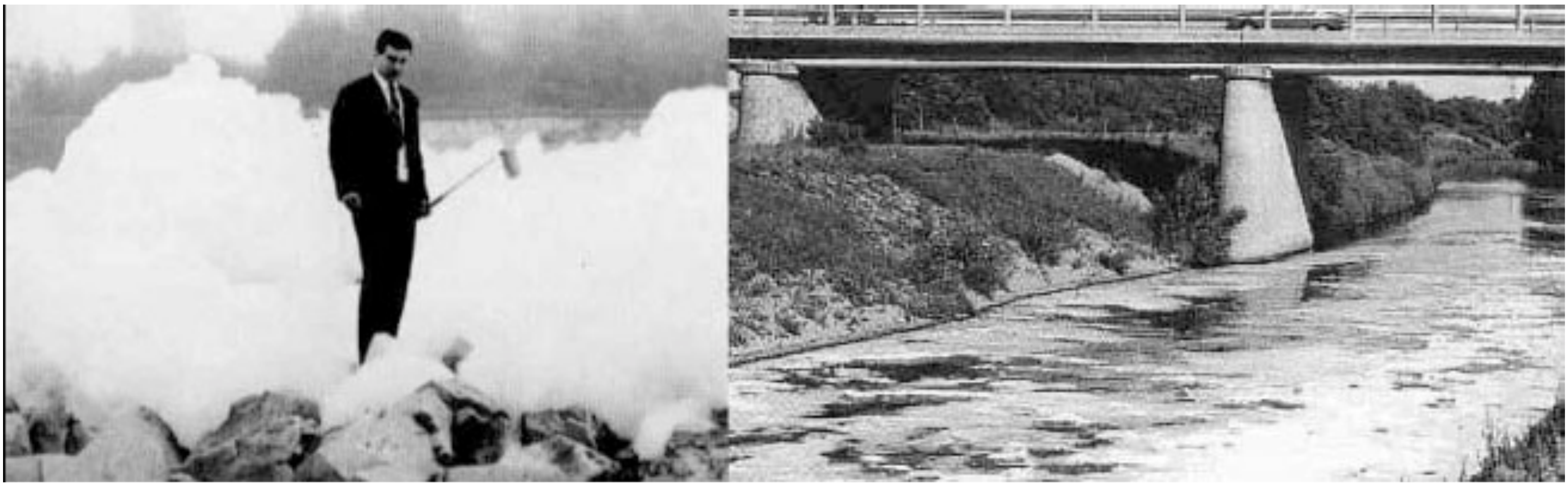
—OH
—OMe
$—NH_2$
—Cl

$—CO_2H$
$—CH_3$
$—CF_3$
$—NO_2$

Benzenesulfonate Anionic Surfactants

- “Workhorse” surfactant in laundry detergents
- Tetrapropylenebenzenesulfonate (TPBS) degraded only about 50% in sewage (POTW) treatment
- LAS replaced TPBS in detergents in the 1960s
- Illustrate biodegradability rules of thumb: greatly reducing the amount of alkyl chain branching yields higher biodegradability
- Linear alkylbenzenesulfonate (LAS) removal >98%

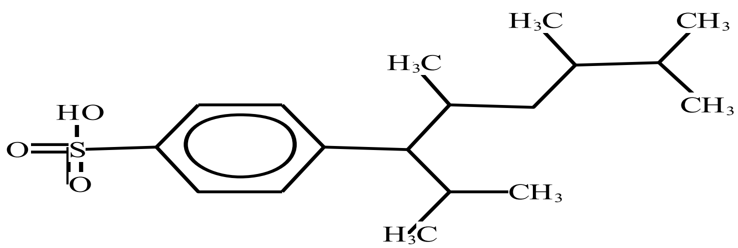
Downstream from the POTW in the 1950s…..



Source: Henkel Co. archives, via Klaus Kümmerer 2007 (*Green Chemistry* 9:899-907)

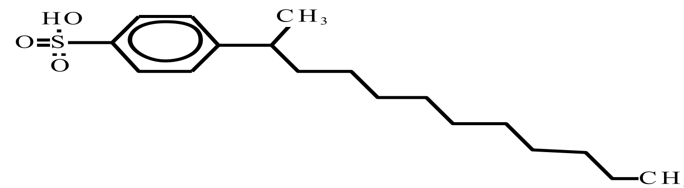
Benzenesulfonate Anionics cont.

TPBS



- ►Yields clean laundry
- ►In extreme cases, POTW staff asphyxiated (i.e., KILLED) after slipping from walkways and falling into foaming tanks
- ►Reduced efficiency of treatment plants
- ►Increased dispersal of pathogenic bacteria
- ►Water foamed at the tap

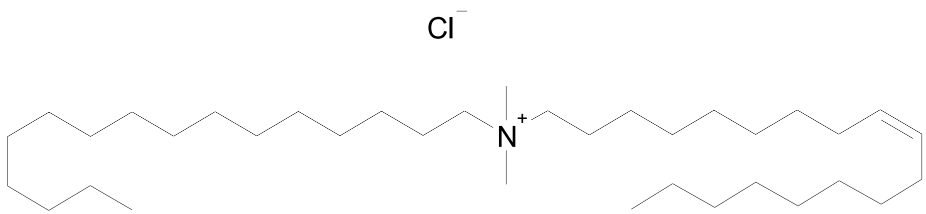
LAS



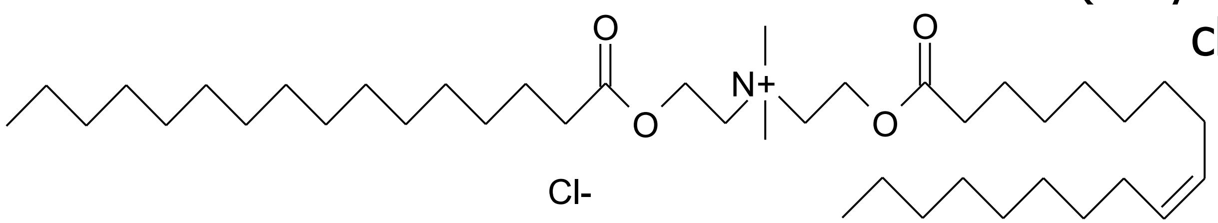
- ►Yields clean laundry
- ►Very biodegradable—none of the problems shown at left

Your choice!

Fabric Softeners

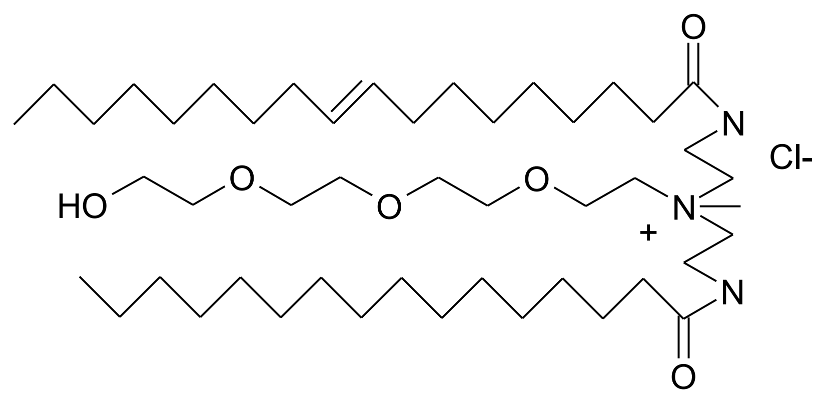


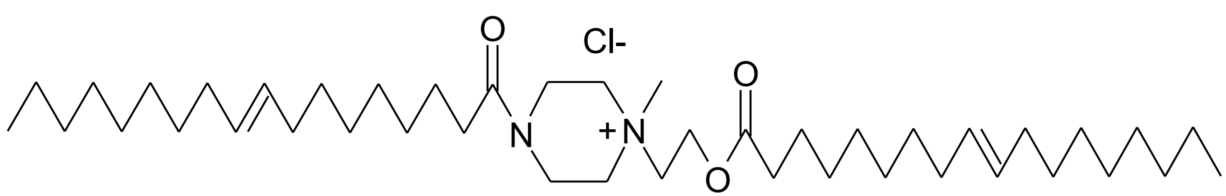
Ditallowdimethylammonium chloride (DTDMAC)



Di(ethyl ester)dimethylammonium chloride (DEEDMAC)

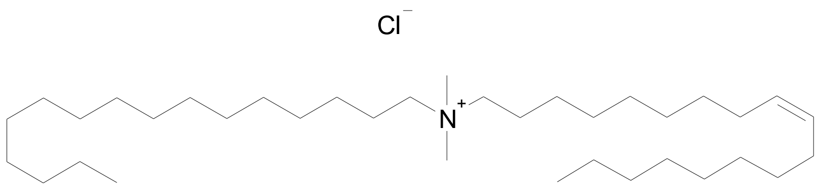
Ethoxylated ethanaminium quaternary ammonium chloride (EEQAC)(4 EO shown)

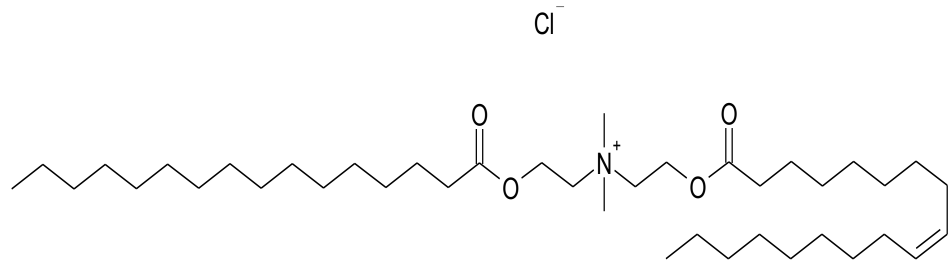




Piperazine-based ester-amide quaternary

Fabric Softeners cont.





Ditallow Dimethyl Ammonium Chloride (DTDMAC)

- Poor biodegradability. Accumulates in aquatic sediments
- Voluntary phase-out in some European countries
- Cationic surfactants may be highly toxic to aquatic organisms

Diethyl Ester Dimethyl Ammonium Chloride (DEEDMAC)

- Ester linkages increase rate of biodegradation
- Ester quats used in Europe to replace phased-out cationic surfactants in fabric softeners
- Other applications include hair conditioners, lubricants for oil drilling (P&G), textile auxiliaries (e.g. fiber finishes)

Biodegradability of Dialkyl QACs

		Test result	
QAC	**Hydrolyzable group**	**Ready biodeg**	**River die-away**
DTDMAC	none	0-5%	10-20% in 63d 70% in 40d
EEQAC	amide	31%	24-33% in 138d
DEEDMAC	ester	76%	$T_{1/2}$ = 1.1d

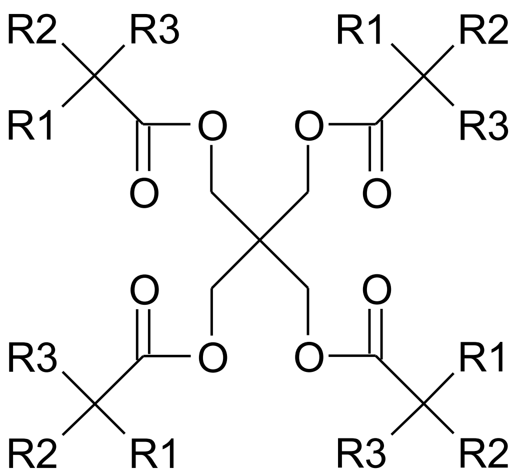
Functional Fluids

- "Functional fluids" = hydraulic fluids; transformer oils; lubricating oils
- In transformers, PCBs replaced by mineral oils, silicones, synthetic polyol esters
  - Biodegradability varies but mostly poor
- Esters from seed oils (e.g. canola oil triglycerides) and estolides emerging as biodegradable alternatives

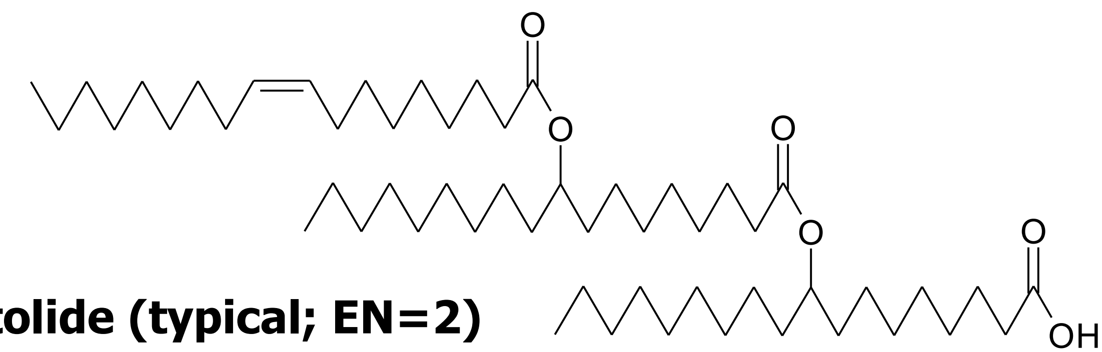
Vegetable Oil and Estolides as Dielectrics

- Vegetable (seed) oil dielectrics
  - Have been problematic due to poor oxidation stability and low temperature performance
  - Better transformer design and additives (e.g. antioxidants and pour point depressants) help
  - High oleic/reduced linoleic acid content also helps make more practical
- Estolides
  - As biodegradable as seed (e.g. canola) oil, but better functional properties. Need fewer additives
  - Fatty acids can be derived from multiple sources

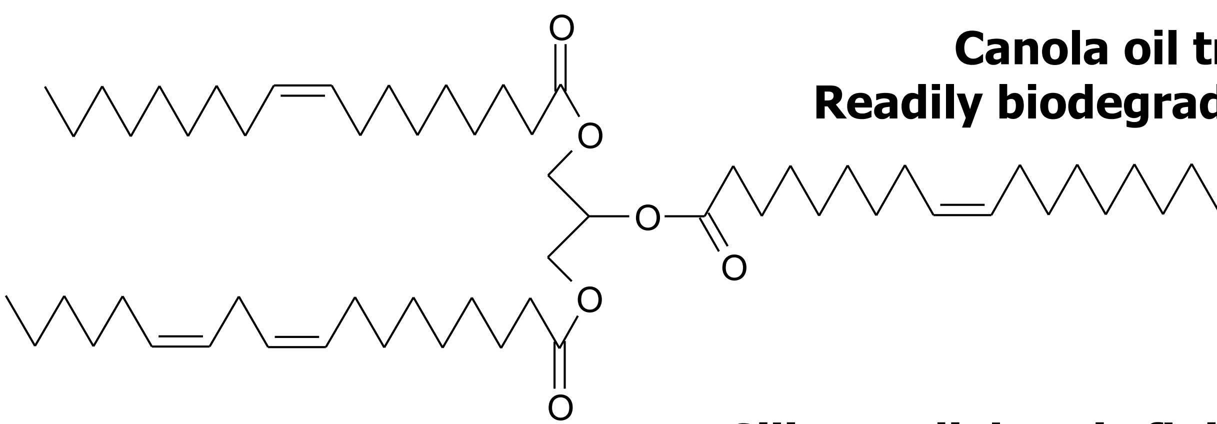
Functional Fluids



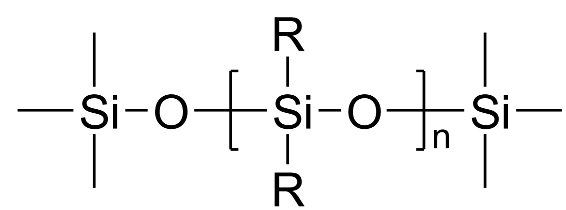
Pentaerythritol polyol ester (generic)
Biodegradable but not readily



Estolide (typical; EN=2)
Readily biodegradable
(301B >80%)



Canola oil triglyceride (typical)
Readily biodegradable (301B 81%; >85%)

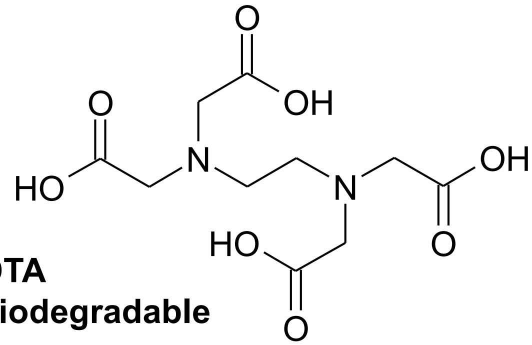


Silicone dielectric fluid (generic)
Not biodegradable

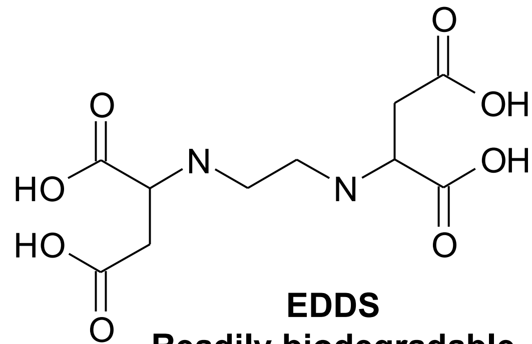
Functional Fluids take home

- Data consistent with rules of thumb: incorporate ester and reduce branching
- Ester-based fluids: think of them as hydrocarbon 'edited' for biodegradability
- Estolides
  - May reduce use of poorly degradable additives like 2,6-di(tert)butylphenol
  - Are they best overall in performance, biodegradability and sustainability?

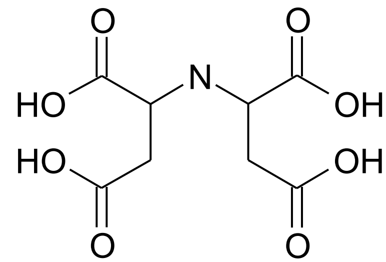
Chelants/Sequestrants



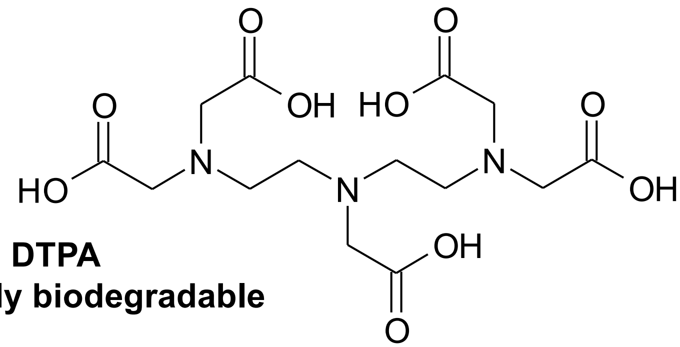
EDTA
Not readily biodegradable



EDDS
Readily biodegradable
([S,S] only)

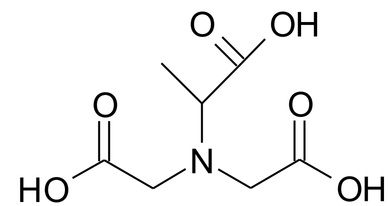


IDS
Readily biodegradable

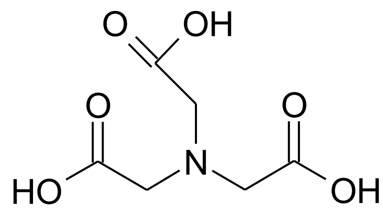


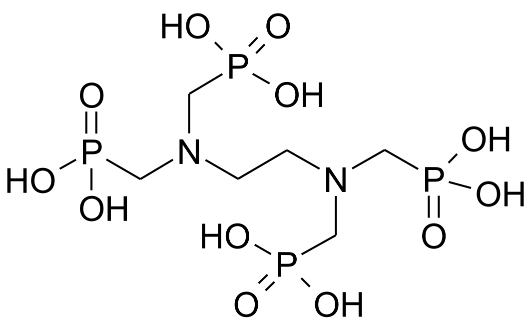
DTPA
Not readily biodegradable

NTA
Biodegradable but not readily degradable

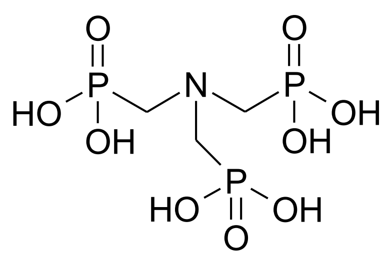


MGDA
Readily biodegradable

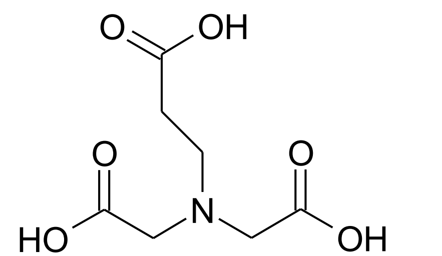




EDTMPA
Not readily biodegradable

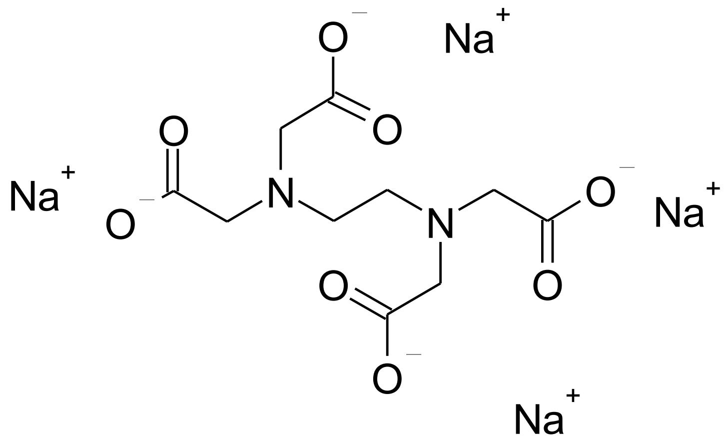


ATMPA
Not readily biodegradable



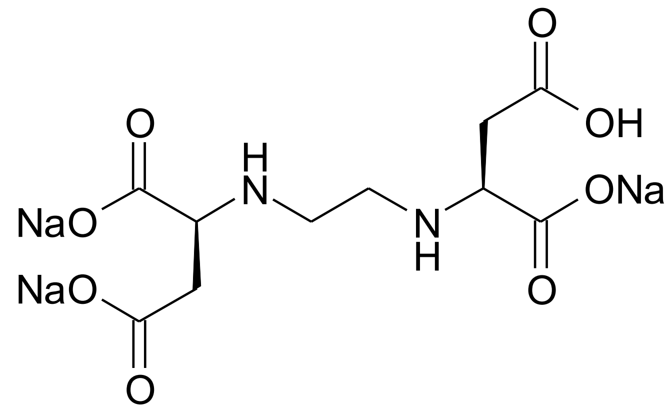
B-ADA
Biodegradable but not readily degradable

Sequestrants



Tetrasodium EDTA

- Environmentally persistent
- Contributes to metal loading of the environment



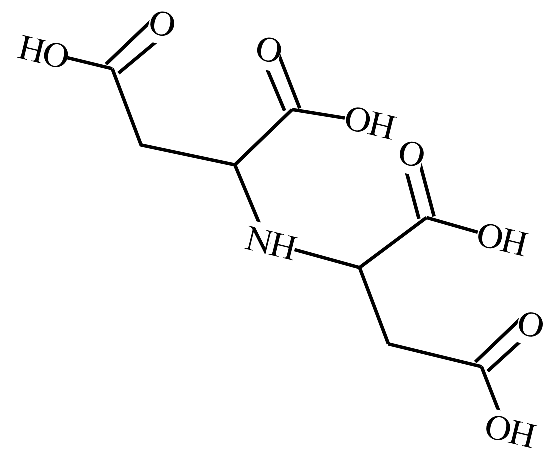
Tri-sodium [S,S]-EDDS, also known as Octaquest™

- Close analog of EDTA
- Readily biodegradable
- Winner of UK Award for Green Chemical Technology

Look closely to see the difference! EDTA has two tertiary amines: *may* be associated with lower biodegradability. EDDS does not and [S,S] stereoisomer is readily degradable

Sequestrants cont.

IMINODISUCCINATE (IDS)



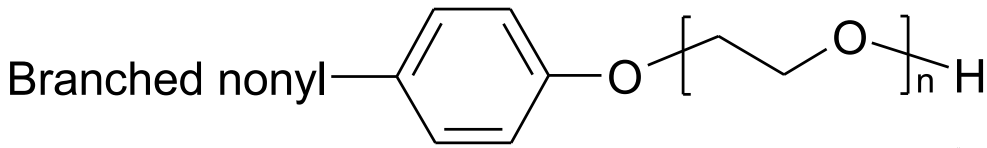
- Baypure™ CX: Bayer Corp.
- Analog of EDDS (Octaquest™)
- Winner of EPA Green Chemistry Award 2001
- Readily biodegradable
- Two times green: not only biodegradable, but the only "waste" product in production is ammonia in water, which is recycled. Nearly all other aminocarboxylate chelants (e.g. EDTA) are made from acetic acid, amines and hydrogen cyanide

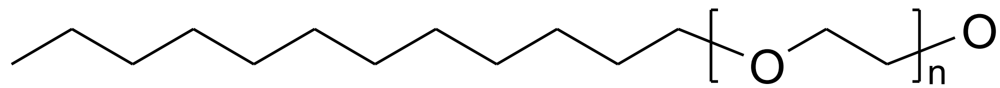
Sequestrants—
Lessons and Complications

- Tertiary amines: generally lower biodegradability

  Pri/sec amine more degradable?
  - EDTA is poorly degradable, but only [S,S] stereoisomer of EDDS is readily degradable
  - Mono-tert amines like NTA are degradable, albeit not readily degradable (except for MGDA, which is)
- Avoid C-P bond: *No* phosphonate sequestrant is readily degradable
- Effect of metal speciation not clear

Polyethoxylate Nonionics





Nonylphenol ethoxylate (NPE) (9.5EO)	**Linear alcohol ethoxylate (LAE) (C10-14, 8EO)**

Nonylphenol ethoxylate (NPE) (9.5EO)

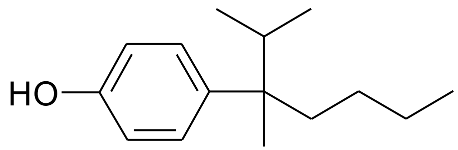
- Highly branched, relatively slow degradation
- Degradation pathways lead through increasingly toxic degradates, possibly including nonylphenol (highly toxic to aquatic organisms; weakly estrogenic)

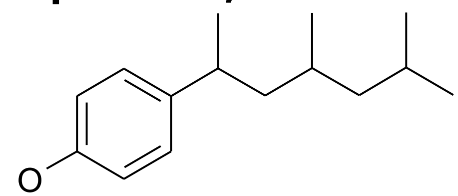
Linear alcohol ethoxylate (LAE) (C10-14, 8EO)

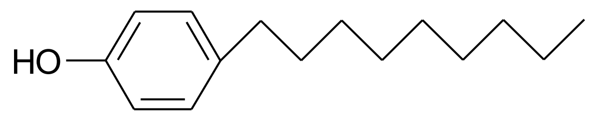
- Quickly and completely biodegradable under all conditions
- Cost-competitive
- Many companies recognized by EPA's DfE Formulator Program have substituted LAEs for NPEs

Nonylphenol Ethoxylates

- Commercial NP dominated by alkyl with quat C;

  i.e. this-- 

  not this-- 

  not this-- 

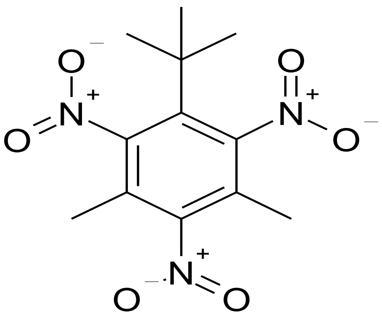
- NPE degradation pathway studies focus on sequential de-ethoxylation and ether carboxylates ("NPECs") as intermediates
- Most isomers can also undergo 1 or 2 beta oxidation cycles
  - Accounts for DeCorcia et al. (1998), who found NPE products degraded from both "ends"
  - Dead-end products resistant to further degradation
  - Predictable from known pathways and rules of thumb

Nonylphenol Ethoxylates: linear vs. branched NP

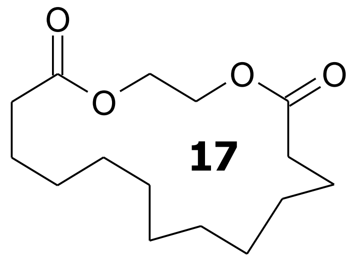
- Linear alkyl offers another route of attack (rapid biodeg--analogy with LAS). There would be no safety issue or controversy
- Linear analog can be made—Ziegler process (olefin from polym. of ethylene)
  - Disadvantages: raw materials and catalyst more expensive; sensitive reaction conditions; etc
- Not a new problem
  - Detergent industry faced—and solved—similar problem with TPBS
  - But NPE uses mainly commercial, not consumer. No visual impact such as river or tap water foaming

Musk Fragrances

- Widely used in detergents, fabric softeners, cleaning products, cosmetics, hand soap, shampoo, perfume, even toothpaste. *All lead to environmental emissions*
- Four major types: nitro, polycyclic, macrocyclic, alicyclic

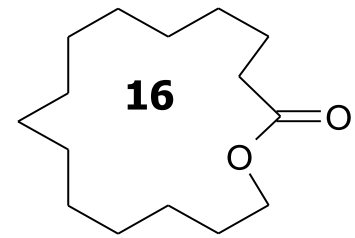


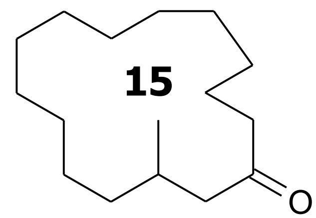
Nitro: musk xylene 81-15-2



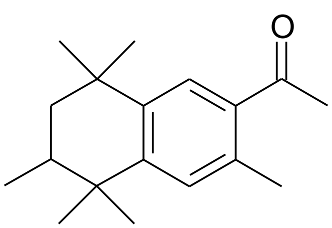
Macrocyclic (lactide): ethylene brassylate 105-95-3

Macrocyclic (lactone): Exaltolide 106-02-5

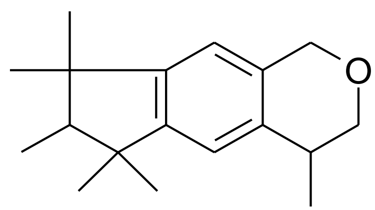




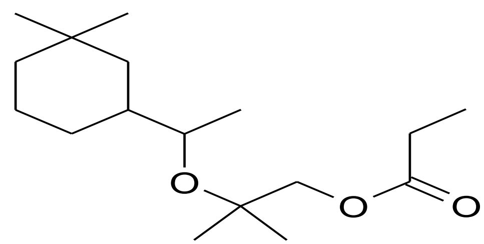
Macrocyclic (ketone): muscone 541-91-3



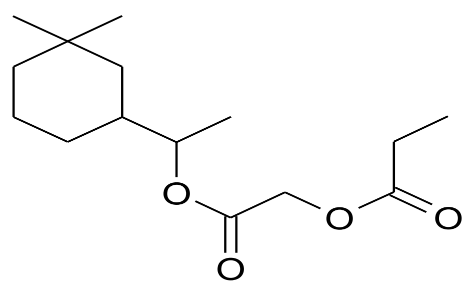
Polycyclic: Tonalide 1506-02-1



Polycyclic: Galaxolide 1222-05-5

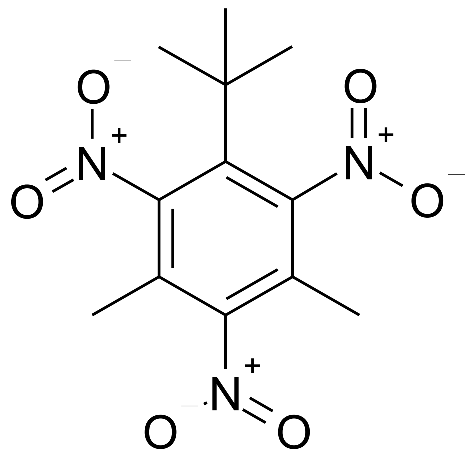


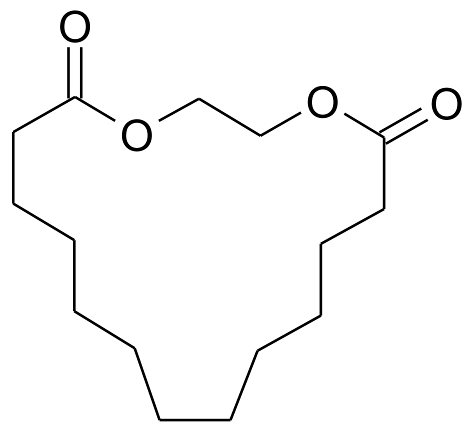
Alicyclic: Helvetolide 141773-73-1



Alicyclic: Romandolide 236391-76-7

Musk Fragrances cont.





Musk xylene

- Appears designed for maximum aerobic persistence—nitro and t-butyl groups; fully substituted ring
- May bioaccumulate
- Potentially toxic to aquatic organisms
- May be an indirect toxicant, inhibiting the ability of cells to excrete harmful chemicals

Ethylene brassylate

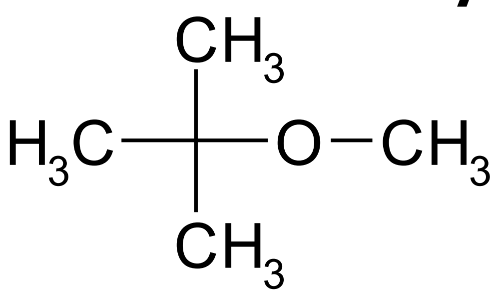
- Faster biodegradation—ester linkages
- Fragrance houses working with EPA’s DfE Formulator Program to replace musk xylene with ethylene brassylate
- Much more expensive than musk xylene. May have different odor profile

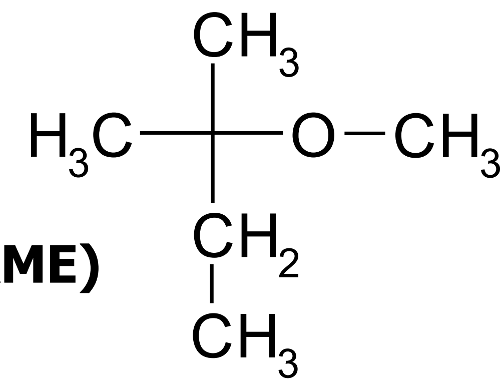
Gasoline Oxygenates - MTBE

- Oxygenates: gasoline additives used to lower CO emissions and boost octane rating
- Methyl tertiary-butyl ether (MTBE) has the highest volume by far: *9 billion kg* in 1999
- MTBE is quite persistent for such a small molecule and has been found repeatedly in ground water
- MTBE's low biodegradability is easily predicted from chemical structure
- Substitutes exist

Oxygenates continued

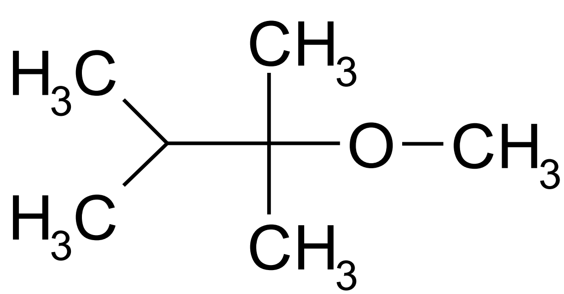
Methyl t-butyl ether (MTBE)



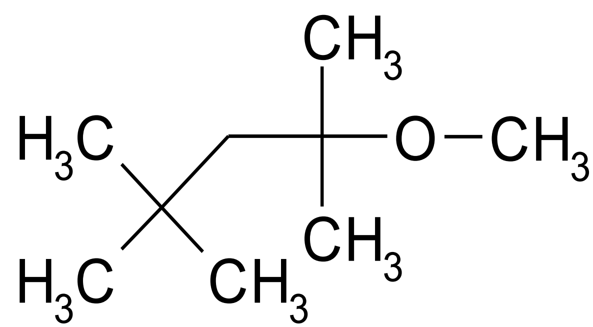


Methyl t-amyl ether (TAME)

Newer ether oxygenates: similar problems expected
(Snelling et al. ET&C 26:2253 (2007))



Methyl t-hexyl ether



Methyl t-octyl ether

Anaerobic Biodegradation of Oxygenates in Aquifer Slurries[a]

Chemical	Octane rating	Acclimation period	Methane, % Theoretical
ethanol	129	25-30	91
isopropanol	118	15-20	112
t-butanol	103	>252	0
methyl ethyl ketone (MEK)	116	15-20	90
acetone	115	25	89
ethyl acetate	117	0-7	94
methyl-t-butyl ether (MTBE)	118	>249	0
methyl-t-amyl ether	111	>182	0
diisopropyl ether	110	>252	0
diethyl ether	--	>182	0
di-n-butyl ether	--	>182	0
methyl-n-butyl ether	--	84	99

[a]Suflita and Mormile (1993)

Challenges of Safe Chemical Design Toxicity vs. Persistence

Advice[a]	Toxicity endpoint/ objective	Effect on persistence
Increase MW to >1000	Lower aquatic tox	Increase
Reduce water solubility to <1 ppb	Lower aquatic tox	Decreases availability to biodegrading enzymes
Increase steric hindrance at active site	Lower aquatic tox	Decreases availability to biodegrading enzymes
Add bulky groups to, or ortho to, amine	Reduce onco concern for aromatic amines	Decreases accessibility to biodegrading enzymes
Add hydrophilic groups; e.g. sulfonate or COOH	Reduce onco concern (enhance excretion)	May increase or decrease

[a]Source: Designing Safer Chemicals, ACS Symp. Series 640

End of Part I

This Presentation, Part II

Include Other Environmental Attributes

- Extend musk fragrances case study
  - Full structural range of synthetic musks
  - Include target substances as well as established commercial products
  - Touch all bases of the PBT paradigm: include aquatic toxicity and bioaccumulation in addition to biodeg
- Show how environmental attributes might be included in screening prior to development or manufacture
- Show how existing predictive tools and knowledge can be used in this screening
- Seek a more holistic perspective on design

Fragrance Design is Complicated

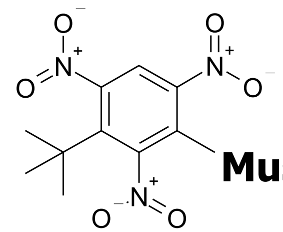
- Seemingly minor changes in chemical structure often profoundly alter odor profile and strength
- Cis/trans isomerism and chirality are important
  - Fragrances may have more than one chiral center
- For musks, there is still no satisfactory chemical structure/odor model, despite >100 years of R&D
- True science and art work hand in hand

"Fragrance chemistry is a fascinating blend of natural product, synthetic, analytical, and physical chemistry with a certain amount of creative fantasy for odours, and molecular structures. Besides the rigor and logic of isolation, analysis and synthesis, one is and should be carried away by serendipitous, artistic, intuitive moods."

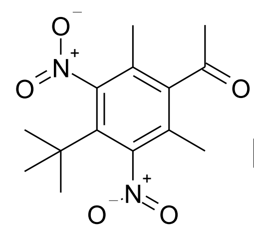
--Fráter et al. *Tetrahedron* 54:7633-7703 (1998)

Nitro and Polycyclic Musks - I

- Nitro musks—first class of artificial musks
  - Discovered by Albert Baur in 1888; he was trying to make improved explosives
  - "Musk Baur" a result of Friedel-Crafts rx'n between toluene and isobutyl bromide ($AlCl_3$ catalyst), then nitration
  - Even stronger-smelling odorants, musk xylene and musk ketone, soon followed

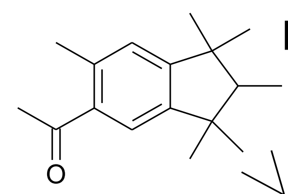


Musk Baur

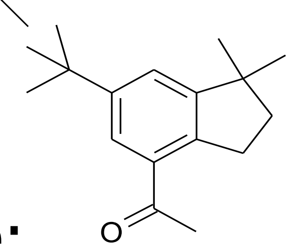


Musk ketone

- Photochemical reactivity and instability under alkaline conditions led to decomposition and discoloration in products
- In the 1950s and 1960s, chemists found replacements in polycyclic compounds
  - The first was Phantolide (1951); others followed
  - Polymethylated indane structures easy to synthesize; hydrophobicity led to good deposition on fabrics



Phantolide



Celestolide

Nitro and Polycyclic Musks - II

- Nitro musks—a “closed chapter” (Fráter et al. 1998)
  - No current production in European Union (SWECO 2008)
  - Musk xylene a candidate PBT substance under OSPAR (2004)
  - Designated vPvB under Annex XV of REACH
  - Not readily biodegradable
- Polycyclic musks—era “approaching an end” (Fráter et al. 1998)
  - Yet Tonalide and Galaxolide are still widely used (are HPV)
  - Found in wastewater, sewage sludge, aquatic biota, human adipose tissue, breast milk in numerous monitoring studies
  - Studies find low environmental risk, but they are bioaccumulative and have high aquatic toxicity
  - Inhibit drug efflux transporters, responsible for multixenobiotic resistance in gills of marine mussels (Luckenbach and Epel 2005)
  - Not readily biodegradable

Methods

- ***Study 1***: musks with measured ready biodegradation data (n=39) and/or measured *Daphnia* (aquatic) acute tox (n=14). None had measured bioaccumulation
  - List of 194 fragrances with measured ready biodegradation data curated from literature and TSCA Premanufacture Notices (PMNs)
  - The list of 194 contained 39 musks in all four major classes
  - 14 musks had measured *Daphnia* 48h EC50. 12 of these also had measured ready biodegradation (were among the 194)
  - Musks were compared relative to environmental attributes: biodegradability, bioaccumulation, aquatic toxicity
- ***Study 2***: extend predictive methods to musks in R&D
  - Assembled a set of 48 structures identified by true experts as promising targets for development. Includes novel structures
  - Applied predictive methods (no test data available for any)

Predictive Methods

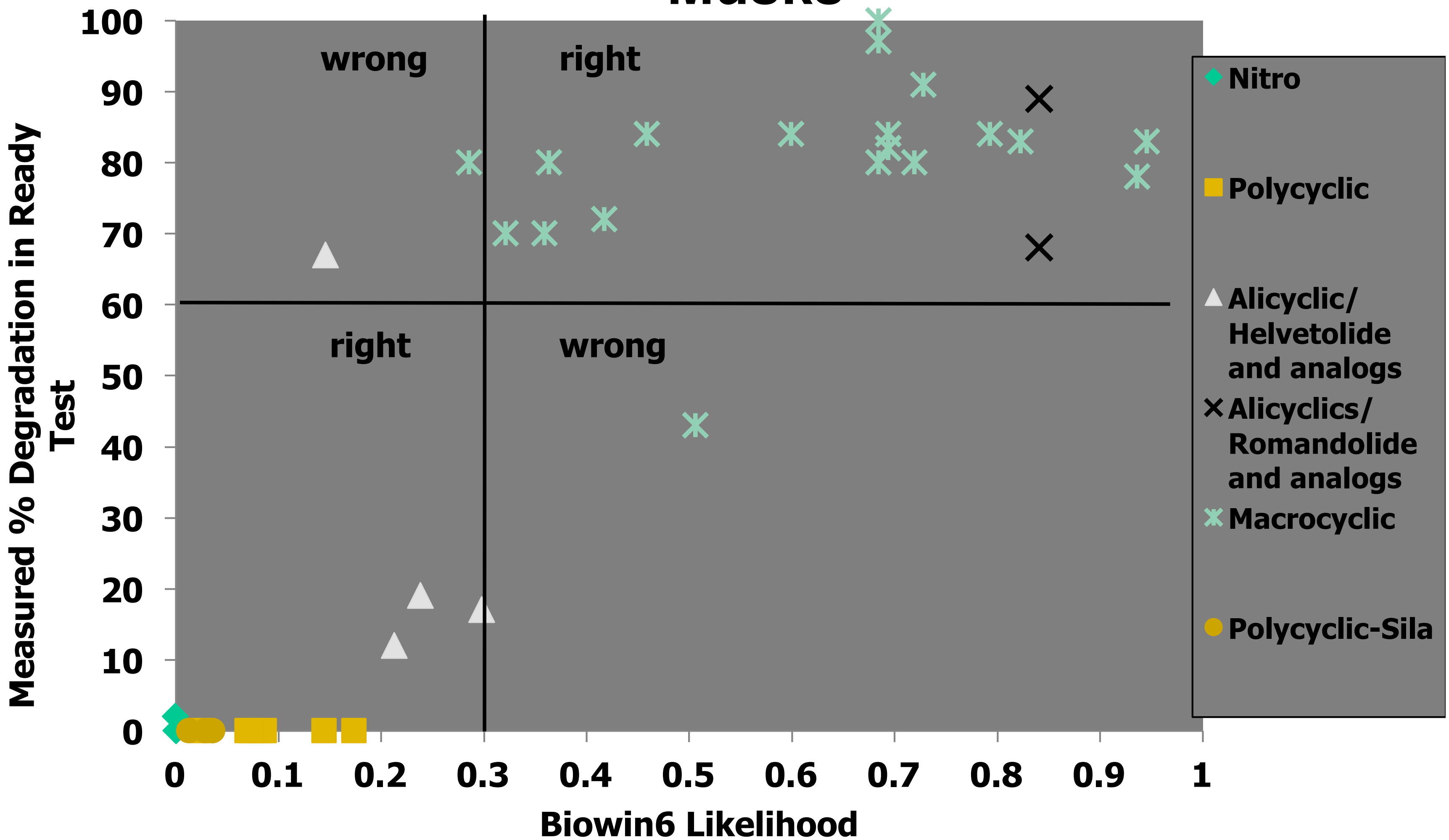
- Biodegradability
  - Likelihood of being readily degradable (RB) in the MITI-I (OECD 301C) test estimated using nonlinear MITI model, BIOWIN6, in EPI Suite v4.10 (Jan 2011)
  - Calculated values >=0.3 taken as predicting RB
- Bioaccumulation in aquatic biota
  - Bioaccumulation factor (BAF) & fish biotransformation half-life estimated using BCFBAF v3.01a, in EPI Suite v4.10
  - BCFBAF incorporates KOWWIN v1.68 and uses it to estimate log K_{OW}, a key input parameter
  - BCFBAF uses the Arnot-Gobas food chain model and includes a model that estimates fish biotransformation

EPI Suite: www.epa.gov/opptintr/exposure/pubs/episuite.htm

Methods: Property Estimation (Cont.)

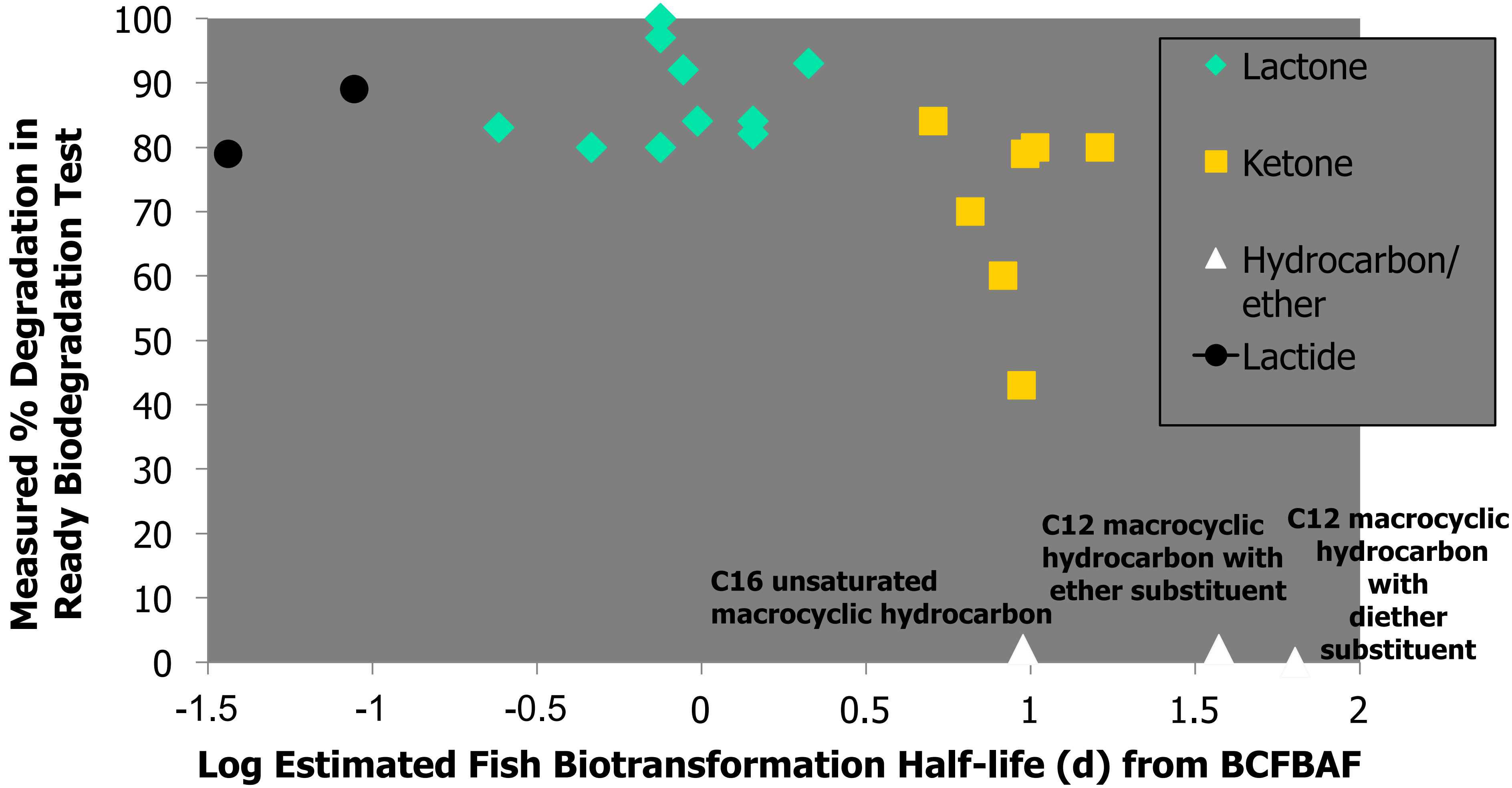
- Bioaccumulation in terrestrial biota
  - Octanol/air partition coefficient (K_{OA}) estimated using KOAWIN v1.10, in EPI Suite v4.10
  - Log K_{OA} >5-6 is an indicator of *potential* for accumulation in air-respiring biota
  - Calculated from air-water (Henry's Law constant) and octanol-water coefficients
- Aquatic toxicity
  - Estimated using ECOSAR v1.00, in EPI Suite v4.10
  - ECOSAR estimates acute and chronic tox using QSARs for neutral organics and multiple chemical classes
  - ECOSAR also available as standalone program at www.epa.gov/oppt/newchems/tools/21ecosar.htm

Measured vs. Predicted Ready Biodegradation of 39 Musks



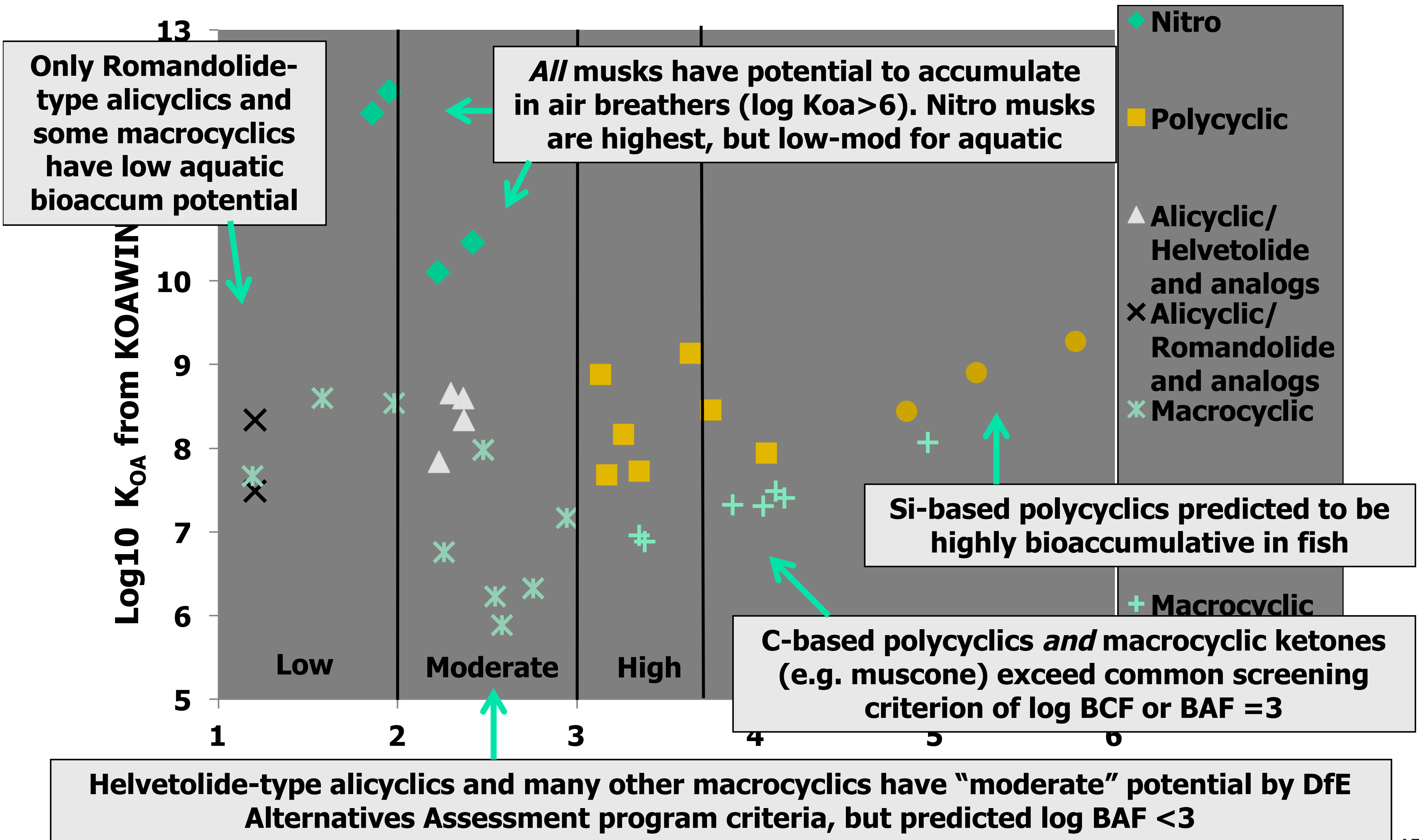
- Except for one, all macrocyclic and Romandolide-type musks are RB
- Except for one, all Helvetolide-type alicyclics, polycyclics (including Si isosteres like disila-Versalide) and nitro musks are NRB
- 36 of 39 musks (92%) correctly predicted by BIOWIN6 model

Measured Ready Biodegradability of Macrocyclic Musks and Related Non-Musk Structures vs. Estimated Fish Biotransformation Half-life

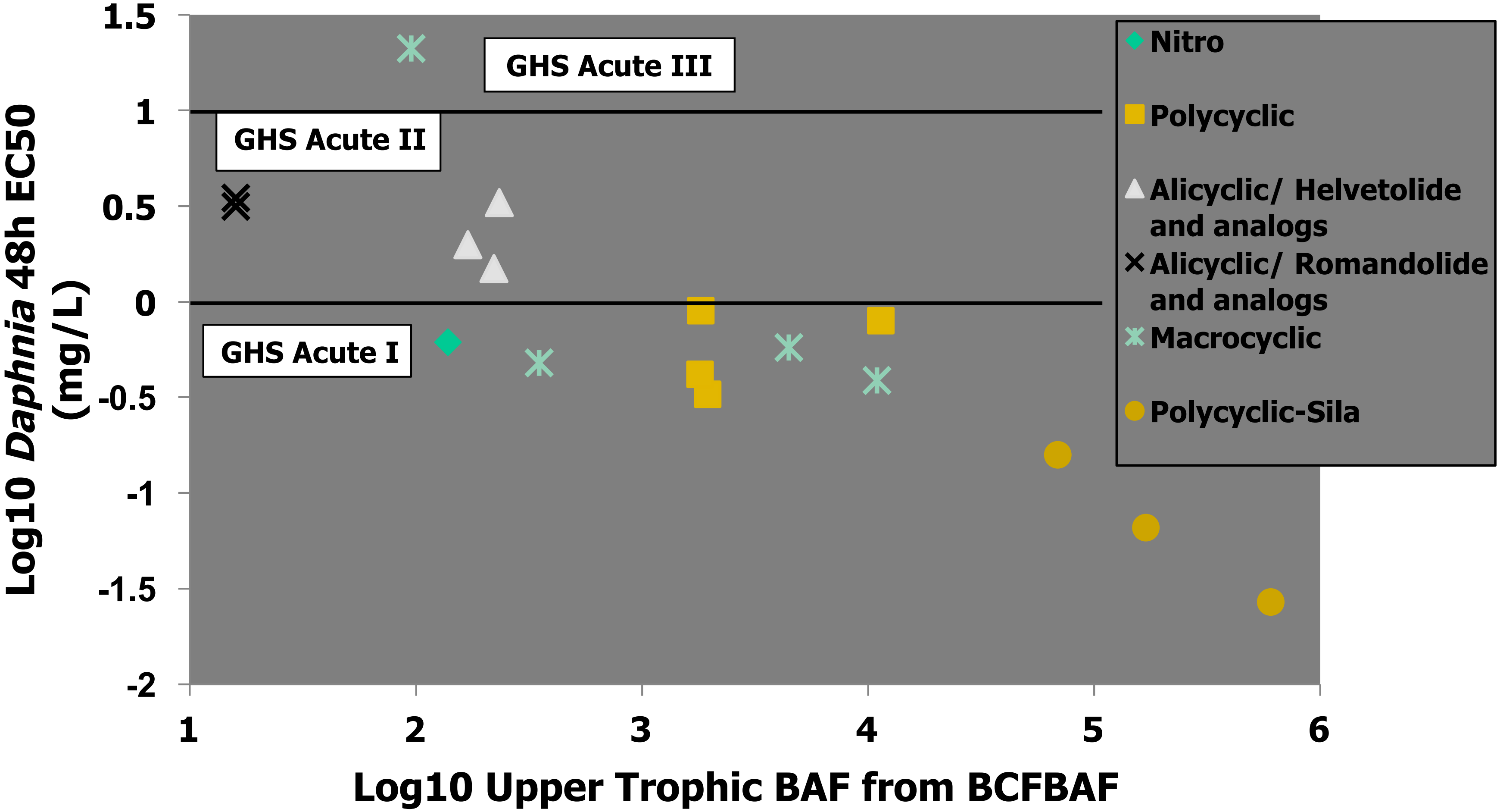


Macrocyclics are RB (one exception), but macrocyclic ketones have somewhat lower % deg, and longer estimated fish metabolism half-lives. Similar ethers and HCs are NRB and more slowly metabolized

Musk Bioaccumulation: Estimated Octanol/Air Coefficient vs. Upper Trophic BAF



Aquatic Toxicity of Musks: Measured Invertebrate (*Daphnia*) Acute vs. Estimated Upper Trophic BAF

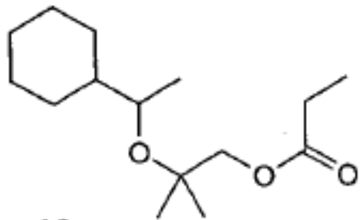


- C-based polycyclics and 3 of 4 macrocyclics had acute tox in highest category (<1 mg/L)
- As a class, alicyclic musks had lowest acute toxicity—but still in moderate range
- Si isosteres had highest acute toxicity (estimated values for these), but they may not be soluble enough to manifest acute effects

Conclusions from Study 1

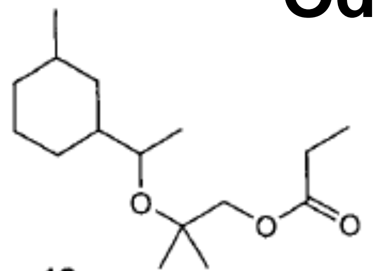
- Among several classes of musk fragrances, Romandolide-type alicyclic musks appear to have the best environmental properties overall: high biodegradability, low bioaccumulation potential, moderate aquatic toxicity
- Silicon-based polycyclic musks appear worst: high aquatic toxicity and bioaccumulation potential, low biodegradability
- Macrocyclics--includes all natural musks– are readily biodegradable but also ecotoxic; may be bioaccumulative
- Helvetolide-type alicyclic and C-based polycyclic musks are not necessarily more toxic or bioaccumulative than macrocyclics, but lower biodegradability makes them appear unattractive
- Ready biodegradation data for musks and related chemicals generally support biodegradability rules of thumb

Study 2: Example Structures from the 48 "Target Odorants"



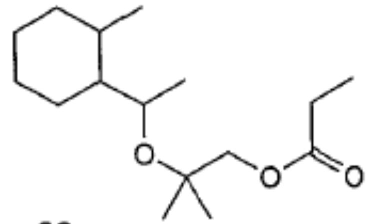
18

musky, erogenous, floral



19

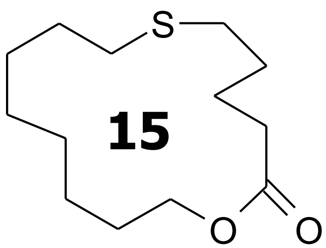
strong musky, floral



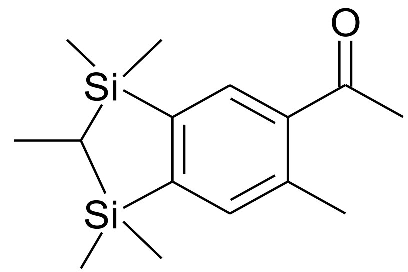
20

musky, natural

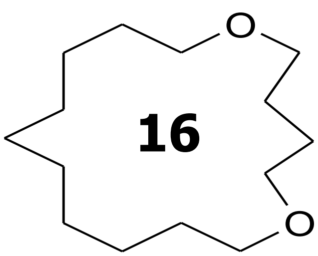
Helvetolide analogs. Source: Eh 2004



Thiamacrolide: "musky, sweet, green". Source: Kraft 2005

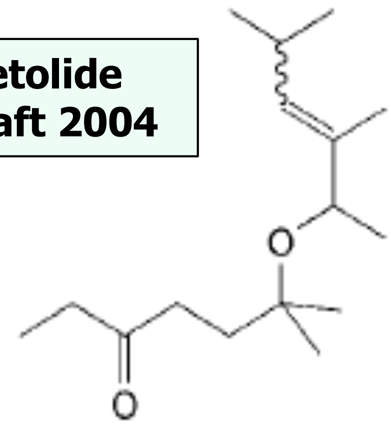


Sila polycyclics: Disila-Phantolide. Source: Metz et al. 2009



Macrocyclic ether: "musky, intense, animalic". Source: Matsuda et al. 2005

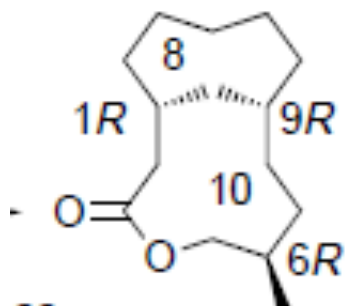
Noncyclic (Helvetolide type). Source: Kraft 2004



37

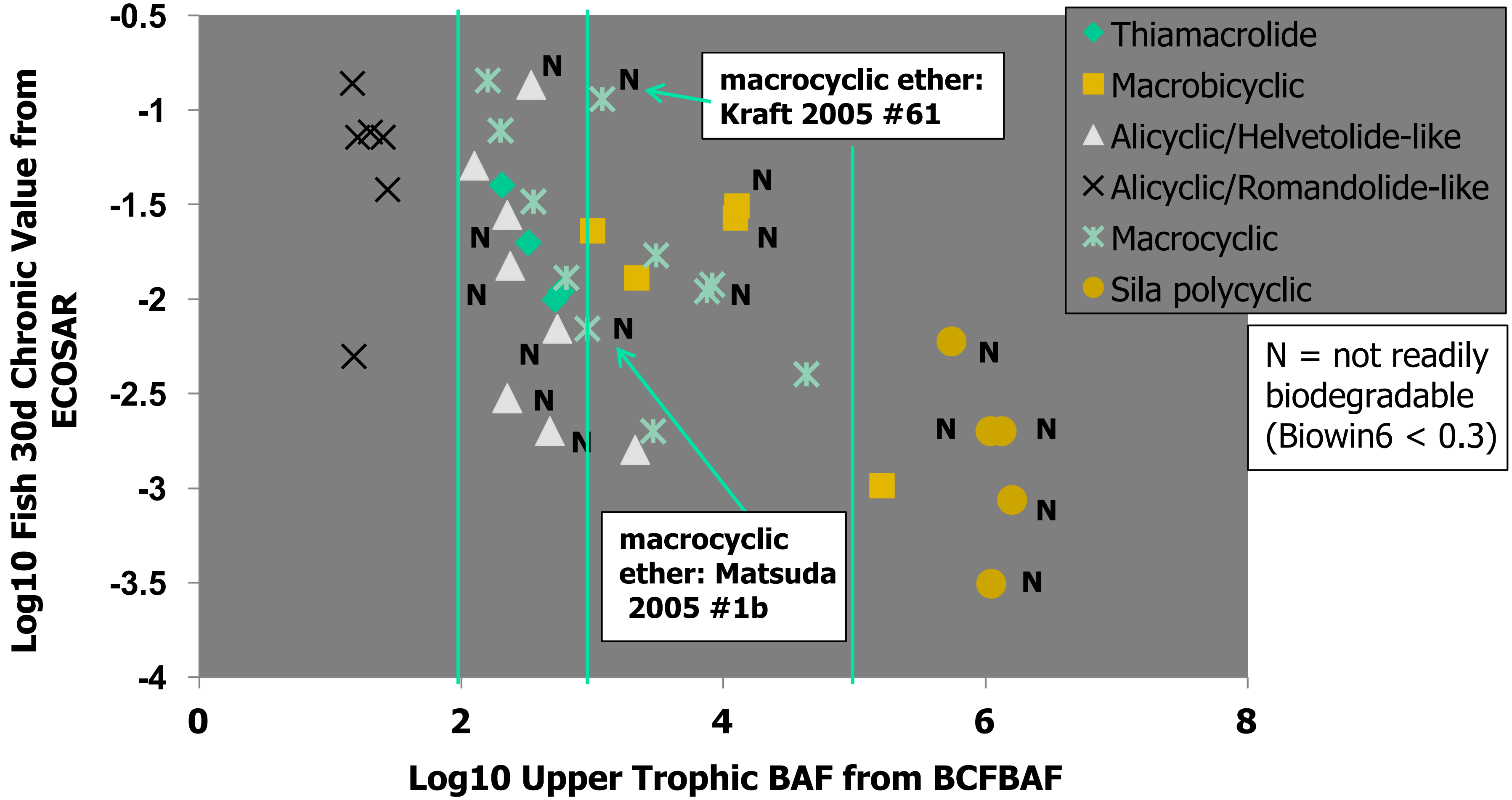
musky, sweet, fruity

Macrobicyclic lactone: "musky, powerful, fresh, anisic, ambery, fruity". Source: Kraft & Cadalbert 2001



22

Musk Design: Estimated Fish Chronic Toxicity, Biodegradability and Upper Trophic BAF for 48 Untested Musks



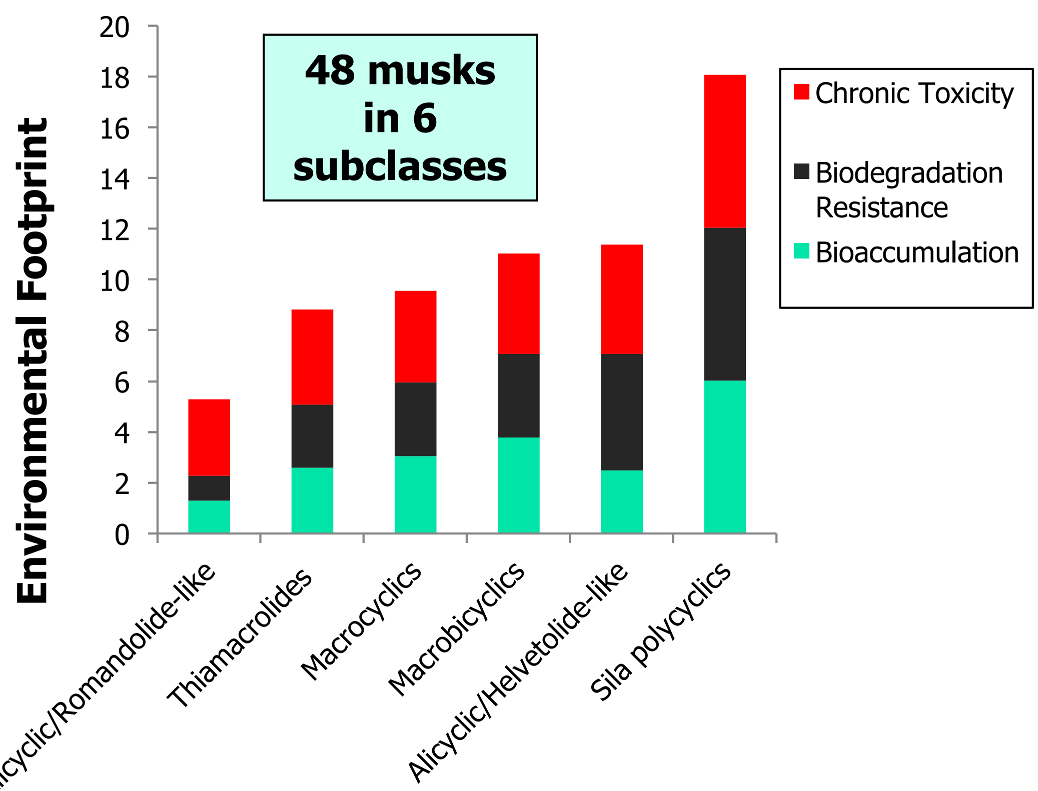
- **As a class, sila polycyclics predicted to be most, and Romandolides least toxic and bioaccumulative**
- **Macrobicyclics and thiamacrolides similar to conventional macrocyclic musks in predicted toxicity and bioaccumulation potential, but note, former more likely to be predicted NRB**
- **Helvetolide class a bit less bioaccumulative than macrocyclics, but 9 of 11 predicted NRB**

Combining and Comparing Attributes by Subclass

- For chemical design purposes it would be useful to have a simple way to express the combined attributes of ecotoxicity, bioaccumulation potential and biodegradability
- One possible metric: Sum averages for the 3 attributes for each subclass

Method:

Calculate for each musk subclass: avg log upper trophic BAFs; avg of logs of reciprocal fish CVs; avg of one minus Biowin6 likelihood value. Scale biodeg and fish CV values to bioaccum for sila polycyclics; therefore equal contributions for P, B and T for this subclass



- **Based on predictive methods, Romandolide-type musks have best properties overall: moderate toxicity, high biodegradability, low bioaccumulation potential. Toxicity may appear as largest negative (red bar)**
- **Sila polycyclic musks are by far the worst**
- **Others are intermediate, but macrocyclics appear less than ideal**

Conclusions from Study 2

"Today, new odorants are...routinely screened for secondary benefits [such as antibacterial activity]" --Gautschi et al. *Chimia* 55:379-387 (2001)

- But there is little published evidence that environmental properties are included in screening.

  If true, why not?
- Existing tools and knowledge make that relatively easy. They are not infallible but allow comparisons
- Information on potential for biodegradability, bioaccumulation and aquatic toxicity can be combined to produce an environmental profile. From this, one class of substances may emerge as more favorable than another

Be Cautious….

- Rules of thumb are only a starting point in design for biodegradability
- Screening-level models like Biowin© are even more crude, and there are no "higher tier" models that predict biodegradability from structure alone. However, tools like Catalogic (http://oasis-lmc.org/products/software/catalogic.aspx) and the EAWAG-BBD Pathway Prediction System (http://eawag-bbd.ethz.ch/predict/aboutPPS.html) can help

►REMEMBER: "All rules of thumb are 'half-truths' at best….but some are useful"

Why Safe Design is Important for New Chemicals

- Prevention is cheaper than recycling, treatment or disposal
- Production, emissions, exposure may increase if a chemical succeeds in the marketplace. If problems arise, they could be impossible to fix
- Difficult to know in advance all possible toxic effects of a new chemical
- New uses often develop, and because they do, emissions and exposure may change
- The global environment is interconnected

Vision

- What happens
  - Past: little or no evident consideration of environmental properties until it is too late. Examples from hindsight: polycyclic and nitro musks
  - Present: we seem to understand the wisdom of respecting the environment, but not necessarily of applying environmental values proactively
- **What we want to see**
  - **Rational design, enabled by knowledge and tools in the earliest phases of R&D, *even before the first flask is filled***
  - **By means of rational design, we avoid making products like polycyclic musks in the first place**