

# Chemical Selection Planning

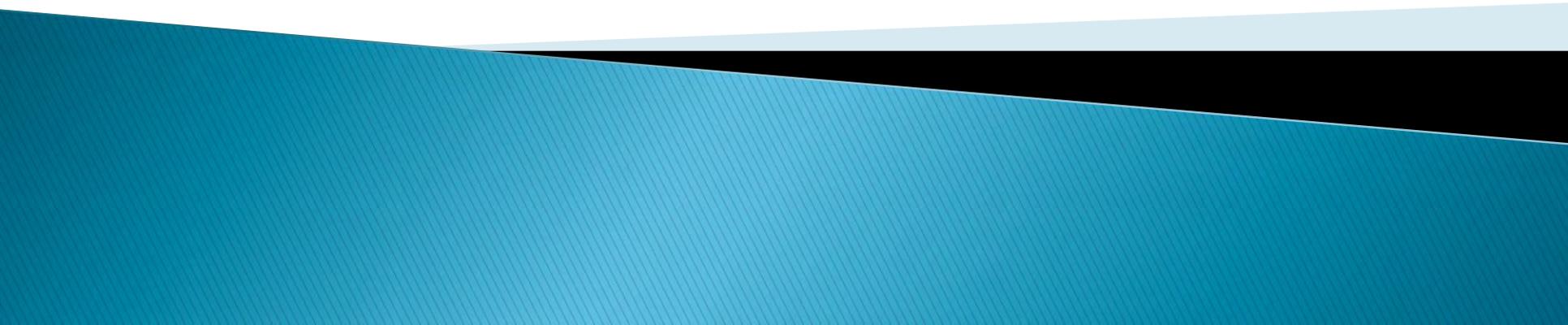
## *Synthetic Musks*

Gail Krowech, Ph.D.

Office of Environmental Health Hazard Assessment

*Presentation to Scientific Guidance Panel*

*November 8, 2012*



# Background

- ▶ Program asked to look into synthetic musks as possible candidates for biomonitoring by:
  - State staff
  - Public
  - Scientific Guidance Panel
- ▶ Purpose of agenda item:
  - Preliminary review of some information on potential exposure

# Synthetic musks

Widely used in personal care and some cleaning products

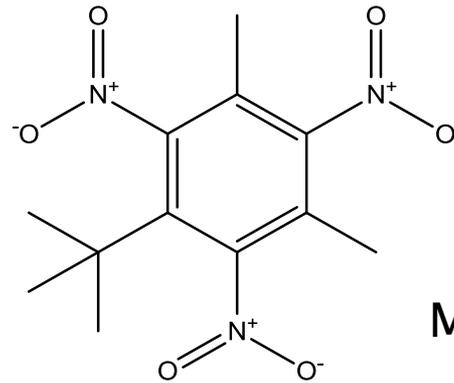
- ▶ Perfume
- ▶ Body lotion
- ▶ Deodorant
- ▶ Shaving cream, soap, body wash
- ▶ Shampoo and conditioner
- ▶ Furniture polish, laundry detergent, fabric softener

Four classes:

- ▶ Nitromusks
- ▶ Polycyclic musks
- ▶ Macrocyclic musks
- ▶ Alicyclic musks

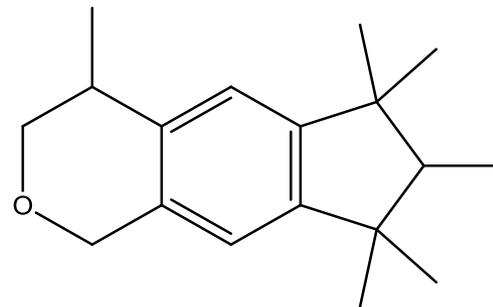
# Example structures

## Nitro musks



Musk xylene

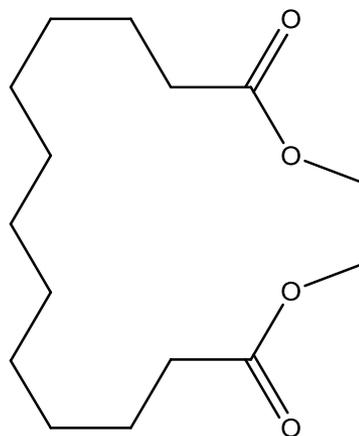
## Polycyclic musks



Galaxolide<sup>®</sup>

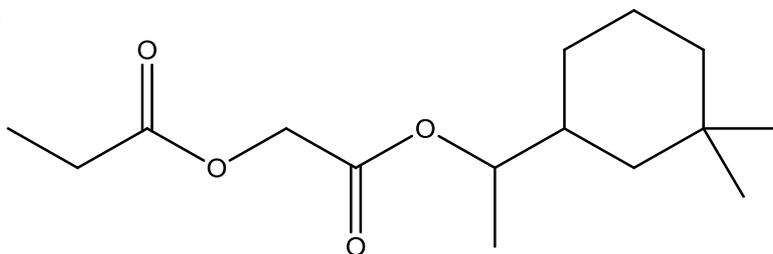
# Example structures (cont.)

- ▶ Macrocyclic musks



Musk T  
(ethylene brassylate)

- ▶ Alicyclic musks



Romandolide®

# Nitro musks

- ▶ Musk xylene and musk ketone most important commercially
- ▶ Declining use worldwide since late 1980s

## U.S. EPA Inventory Update Reporting (pounds)

|             | 1986    | 1990    | 1994    | 2002    | 2006  |
|-------------|---------|---------|---------|---------|-------|
| Musk xylene | 500K–1M | 10–500K | 10–500K | 10–500K | <500K |
| Musk ketone | 10–500K | 10–500K | 10–500K | 10–500K | NR*   |

\*NR=not reported. Import/production volume less than U.S. EPA reporting threshold.

# Nitro musks (cont.)

- ▶ Persistent, bioaccumulative
  - Musk xylene concluded to be very Persistent, very Bioaccumulative (vP,vB) by the EU under REACH

| Chemical    | Persistence<br><i>PBT Profiler* estimate</i> | BCF | Log K <sub>ow</sub> |
|-------------|--|-----|---------------------|
| Musk xylene | <b>Very persistent</b>                       | 400 | 4.45                |
| Musk ketone | <b>Persistent</b>                            | 83  | 4.30                |

\*U.S. EPA screening tool

- ▶ Found in blood, breast milk, adipose tissue and environmental samples

# Polycyclic musks

- ▶ Replacements for nitro musks
- ▶ Galaxolide<sup>®</sup> and Tonalide<sup>®</sup> have been commercially most important

| U.S. EPA Inventory Update Reporting<br>(pounds) |         |         |       |       |       |
|---|---------|---------|-------|-------|-------|
|   | 1986    | 1994    | 1998  | 2002  | 2006  |
| Galaxolide <sup>®</sup>                         | 500K–1M | 1–10M   | 1–10M | 1–10M | 1–10M |
| Tonalide <sup>®</sup>                           | 10–500K | 10–500K | 1–10M | NR*   | NR*   |

# Polycyclic musks (cont.)

- ▶ Analysis of 60 consumer products collected in Albany NY found levels of Galaxolide® as high as:

|                             |                             |
|-----------------------------|-----------------------------|
| 4,990 ppm in body splash    | 1,230 ppm in shaving cream  |
| 3,740 ppm in body lotion    | 1,010 ppm in perfume        |
| 2,250 ppm in antiperspirant | 646 ppm in furniture polish |
- ▶ Individual product may contain more than one musk
  - Perfume sample: 1,010 ppm Galaxolide® and 451 ppm Tonalide®

From Reiner and Kannan (2006)

# Polycyclic musks (cont.)

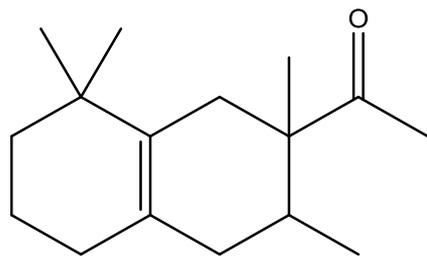
| Chemical    | Persistence<br><i>PBT Profiler* estimate</i> | BCF  | Log K <sub>ow</sub> |
|-------------|--|------|---------------------|
| Galaxolide® | Persistent                                   | 3600 | 5.9                 |
| Tonalide®   | Persistent                                   | 700  | 5.7                 |

\*U.S. EPA screening tool

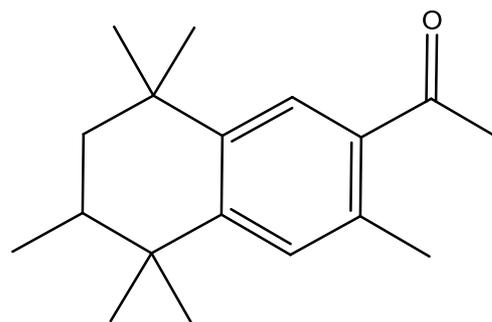
Detected in:

- ▶ House dust
- ▶ Wastewater, fish collected near effluent sites
- ▶ Bivalves in San Francisco Bay
- ▶ Marine mammals
- ▶ Humans: adipose tissue, breast milk, blood

# Structurally-related fragrance: Iso E Super<sup>®</sup>



Iso E Super<sup>®</sup>



Tonalide<sup>®</sup>

## U.S. EPA Inventory Update Reporting (pounds)

|                          | 1986    | 1994    | 1998  | 2002  | 2006  |
|--------------------------|---------|---------|-------|-------|-------|
| Iso E Super <sup>®</sup> | 10-500K | 500K-1M | 1-10M | 1-10M | 1-10M |

# Iso E Super<sup>®</sup> (cont.)

| Chemical                 | Persistence<br><i>PBT Profiler* estimate</i> | BCF         | Log K <sub>ow</sub> |
|--------------------------|--|-------------|---------------------|
| Iso E Super <sup>®</sup> | <b>Persistent</b>                            | <b>1200</b> | 5.18                |

\*U.S. EPA screening tool

Detected in:

- ▶ House dust
- ▶ Wastewater

# Macrocyclic musks

- ▶ Likely an emerging class of musks
- ▶ Available volume of use, in pounds:

|  | U.S. EPA Inventory Update Reporting |           |           |                         | IFRA*<br>North America  |
|--|-------------------------------------|-----------|-----------|-------------------------|-------------------------|
|  | 1986                                | 1994      | 2002      | 2006                    | 2008                    |
| <b>Exactolide</b><br>$\omega$ -pentadecalactone                    | 10 - 500K                           | 10 - 500K | 10 - 500K | <500K                   | ~200K - 2M              |
| <b>Habanolide</b><br>E- and Z-Oxacyclohexadec-<br>12(+13)-en-2-one | NR                                  | NR        | NR        | 1 - 10M<br>(one isomer) | ~200K - 2M<br>(mixture) |
| <b>Muskonate</b><br>Ethylene dodecanedioate                        | NR                                  | 10 - 500K | 10 - 500K | <500K                   | ~200K - 2M              |
| <b>Musk T</b><br>Ethylene brassylate                               | NR                                  | 10 - 500K | 500K - 1M | 500K - 1M               | ~200K - 2M              |

\*International Fragrance Association (2008). Volume of use reported in Salvito et al. (2011)

# Macrocyclic musks (cont.)

Industry toxicity reviews by RIFM\* published in 2011 on each of the following:

| <i>Lactones/lactides</i>   | <i>Ketones</i>  |
|--|---|
| <ul style="list-style-type: none"><li>• ethylene brassylate</li><li>• ethylene dodecanedioate</li><li>• hexadecanolide</li><li>• <math>\omega</math>-6-hexadecenlactone</li><li>• 16-hydroxy-7-hexadecenoic acid lactone</li><li>• 10-oxahexadecanolide</li><li>• 11-oxahexadecanolide</li><li>• 12-oxahexadecanolide</li><li>• oxacycloheptadec-10-ene-2-one</li><li>• oxacyclohexadecane-2,13-dione</li><li>• E- and Z-oxacyclohexadec-12(+13)-en-2-one</li><li>• <math>\omega</math>-pentadecalactone</li></ul> | <ul style="list-style-type: none"><li>• cyclopentadecanone</li><li>• cyclohexadec-8-en-1-one (mixture of cis and trans isomers)</li><li>• 3-methylcyclopentadecanone (mixed isomers)</li><li>• 4-cyclopentadecen-1-one, (Z)-</li><li>• 4-cyclopentadecen-1-one</li><li>• E- and Z-oxacyclohexadec-12(+13)-en-2-one</li><li>• 3-methyl-1-cyclopentadecanone</li><li>• cyclohexadecanone</li><li>• cycloheptadeca-9-en-1-one</li><li>• 5-cyclohexadecen-1-one</li></ul> |

\*RIFM – Research Institute for Fragrance Materials

# Macrocyclic musks (cont.)

- ▶ Persistence, bioaccumulation predictions:

| Chemical                | Persistence                   | BCF  | Log K <sub>ow</sub> |
|-------------------------|-------------------------------|------|---------------------|
|                         | <i>PBT Profiler estimate*</i> |      |                     |
| Exactolide <sup>®</sup> | Not Persistent                | 5300 | 6.15                |
| Habanolide <sup>®</sup> | Not Persistent                | 770  | 4.88                |
| Muskonate <sup>®</sup>  | Not Persistent                | 280  | 4.22                |
| Ethylene brassylate     | Not Persistent                | 600  | 4.71                |

\*U.S. EPA screening tool

- ▶ Ethylene brassylate detected in house dust

# Alicyclic musks

- ▶ Another emerging class of musks?
- ▶ U.S. production/import volume (2006) for Helvetolide<sup>®</sup> reported as <500,000 pounds

| Chemical                 | Persistence                   | BCF   | Log K <sub>ow</sub> |
|--------------------------|-------------------------------|-------|---------------------|
|                          | <i>PBT Profiler* estimate</i> |       |                     |
| Helvetolide <sup>®</sup> | Persistent                    | 2000  | 5.51                |
| Romandolide <sup>®</sup> | Persistent                    | 400   | 4.45                |
| Cyclomusk                | Persistent                    | 14000 | 6.76                |

\*U.S. EPA screening tool

# Synthetic musks in house dust

- ▶ Samples collected as part of the Canadian House Dust Study, 2007–2010 (n=49)

|                                       |                                  | Household vacuum cleaner dust , ppb |        |      |        |
|---------------------------------------|----------------------------------|-------------------------------------|--------|------|--------|
|                                       |                                  | Detection Frequency                 | Median | Min  | Max    |
| <i>Nitro musks</i>                    | Musk xylene                      | 98                                  | 41     | n.d. | 2,130  |
|                                       | Musk ketone                      | 69                                  | 45     | n.d. | 559    |
| <i>Polycyclic musks</i>               | Galaxolide <sup>®</sup>          | 100                                 | 992    | 36   | 31,100 |
|                                       | Galaxolide <sup>®</sup> -lactone | 100                                 | 492    | 76   | 2,190  |
|                                       | Tonalide <sup>®</sup>            | 100                                 | 405    | 91   | 2,360  |
| <i>Structurally-related fragrance</i> | Iso E Super <sup>®</sup>         | 82                                  | 212    | n.d. | 5,620  |
| <i>Macrocyclic musk</i>               | Ethylene brassylate              | 43                                  | n.d.   | n.d. | 1,030  |

Kubwabo et al. (2012)

# Biomonitoring – blood, adipose

|   | N   | Galaxolide® |           | Tonalide® |          | Musk xylene  |          |
|---|-----|-------------|-----------|-----------|----------|--------------|----------|
|   |     | % detected  | Range     | %         | Range    | %            | Range    |
| <i>Blood (ng/L)</i>                                   |     |             |           |           |          |              |          |
| Hutter et al. 2009<br>median 23 yrs<br>Austria        | 100 | 91          | nd – 4100 | 17        | nd – 800 | 79           | nd – 60  |
| Hutter et al. 2010<br>median 60 yrs, women<br>Austria | 53  | 89          | nd – 6900 | 23        | nd – 290 | 62           | nd – 190 |
| <i>Adipose tissue (ng/g lipid)</i>                    |     |             |           |           |          |              |          |
| Kannan et al. 2005<br>New York City                   | 49  | 100         | 12–798    | 86        | <8–134   | Not measured |          |

# Biomonitoring – breast milk, U.S.

| Number of children previously nursed | Galaxolide | Galaxolide-lactone | Tonalide | Musk xylene | Musk ketone |
|--------------------------------------|------------|--------------------|----------|-------------|-------------|
| <i>ng/g lipid</i>                    |            |                    |          |             |             |
| <b>0 (n = 31)</b>                    |            |                    |          |             |             |
| Mean                                 | 227        | 58.3               | 55.5     | 29.2        | 83.3        |
| Median                               | 136        | 58.3               | 53       | 17.0        | 58.2        |
| Max                                  | 917        | 88.0               | 144      | 150         | 212         |
| <b>1 or more (n =7)</b>              |            |                    |          |             |             |
| Mean                                 | 139        | <10                | 29.9     | *           | 25          |
| Median                               | 121        | <10                | 18.6     | *           | 22          |
| Max                                  | 415        | <10                | 73.3     | *           | 49.6        |

\*Only one sample above the detection limit – 39.7 ng/g lipid

Reiner et al. 2007

# Preliminary summary

- ▶ Nitro musks –
  - Use/exposure declining, however still detected
  - Evidence of persistence, bioaccumulation
- ▶ Polycyclic musks –
  - Based on available information, members of this class still appear to be in use; declining use in Europe
  - Evidence of persistence, bioaccumulation

# Preliminary summary (cont.)

- ▶ Iso E Super<sup>®</sup> (structurally related to Tonalide<sup>®</sup>)
  - Increasing trend in reported volume in U.S. between 1986 and 2006
  - Increasing trend in reported volume in Sweden from 2003 to 2010
  - Predicted to be persistent and bioaccumulative

# Preliminary summary (cont.)

## ▶ Macrocyclic musks

- Likely increasing use, based on 2008 data and declining use of polycyclic musks
- Predicted to be non-persistent
- $\log K_{ow} > 4$

## ▶ Alicyclic musks

- Possibly an emerging class
  - Volume of use data located for only one alicyclic musk (2006)
- Predicted to be persistent, bioaccumulative

# Questions for the Panel

- What would the Panel suggest for next steps?
  - Additional screening of synthetic musks? Other fragrances?
  - Proceeding with potential designated document(s) on particular synthetic musks, classes of musks, or other fragrances?
  - Other ideas?