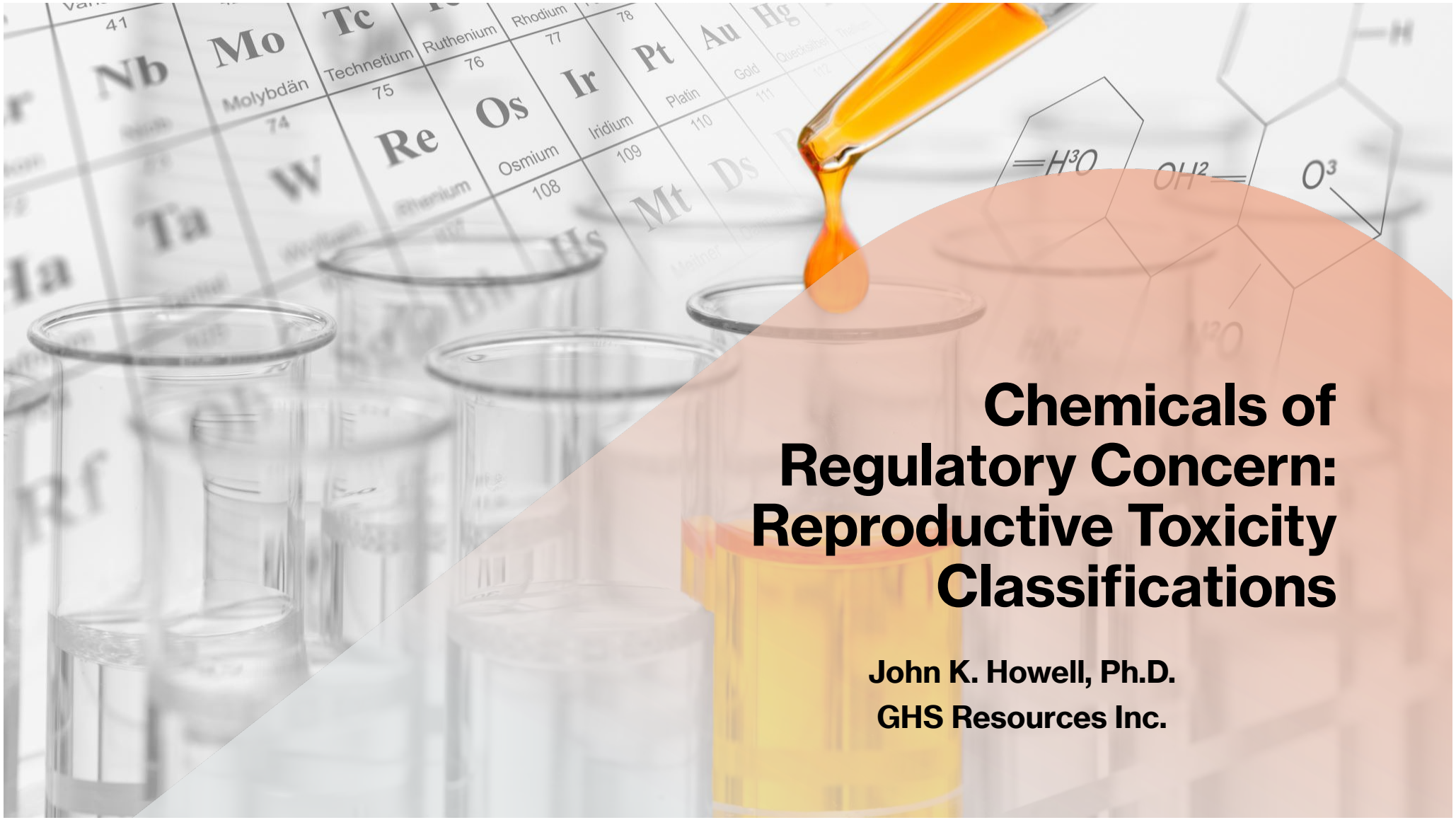

Chemicals of Regulatory Concern: Reproductive Toxicity Classifications

John K. Howell, Ph.D.

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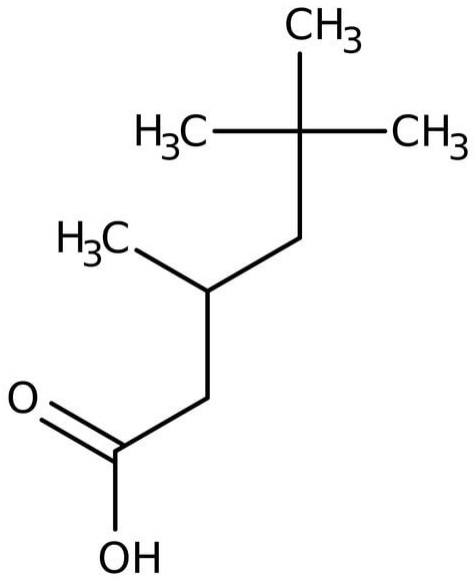
Reproductive Toxicity – Isononanoic Acid

- Isononanoic acid
- 3,5,5-trimethyl
  hexanoic acid
- EC# 221-975-0
- CAS# 3302-10-2
- Proposed: Repro toxicity,
  Category 1B



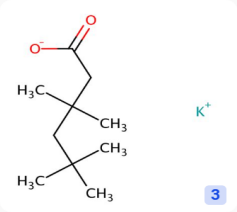
Reproductive Toxicity - Neodecanoic Acid

- Neodecanoic acid
- EC# 248-093-9
- CAS# 26896-20-8
- Possible classification
- Repro toxicity, Category 1B

- **CAS Number**: 26896-20-8 [1] [2].

Components of this mixture include acids with the common property of a “trialkyl acetic acid,” having three alkyl groups at carbon two. Some specific components are:

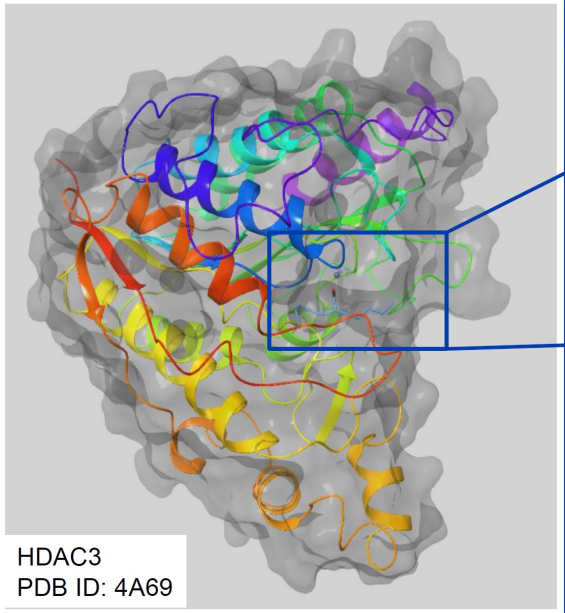
1. **2,2,3,5-Tetramethylhexanoic acid**
2. **2,4-Dimethyl-2-isopropylpentanoic acid**
3. **2,5-Dimethyl-2-ethylhexanoic acid**
4. **2,2-Dimethyloctanoic acid**
5. **2,2-Diethylhexanoic acid** [2].



Reproductive Toxicity – Short Chain, Branched Acids

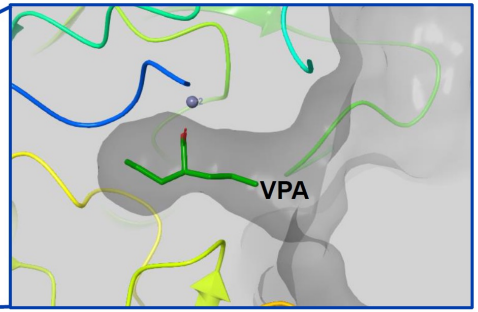
Molecular Docking with Histone Deacetylase

Structure of histone deacetylase 3 (HDAC3)



HDAC3
PDB ID: 4A69

Close up view of HDAC3 binding pocket



HDAC receptor contains two asymmetric binding pockets:

(1) small pocket which only fits a shorter alkyl chain
(2) larger pocket which can tolerate longer alkyl chains

VPA is a good ligand for HDAC3

Human Safety
Ensuring Safe Products

Reproductive Toxicity – Tolyltriazole

- Tolyltriazole
- Mixture of 4- and 5-methyl-1H-benzotriazole
- EC# 249-596-6
- CAS# 29385-43-1
- Harmonized Classification: Repro toxicity, Cat 2 (ECHA)

Reproductive Toxicity – Benzotriazole

- Benzotriazole
- 1H-benzotriazole
- EC# 249-596-6
- CAS# 29385-43-1
- Possible classification as repro toxicant

Reproductive Toxicity – Benzotriazole

Substance Evaluation Conclusion document EC No 202-394-1

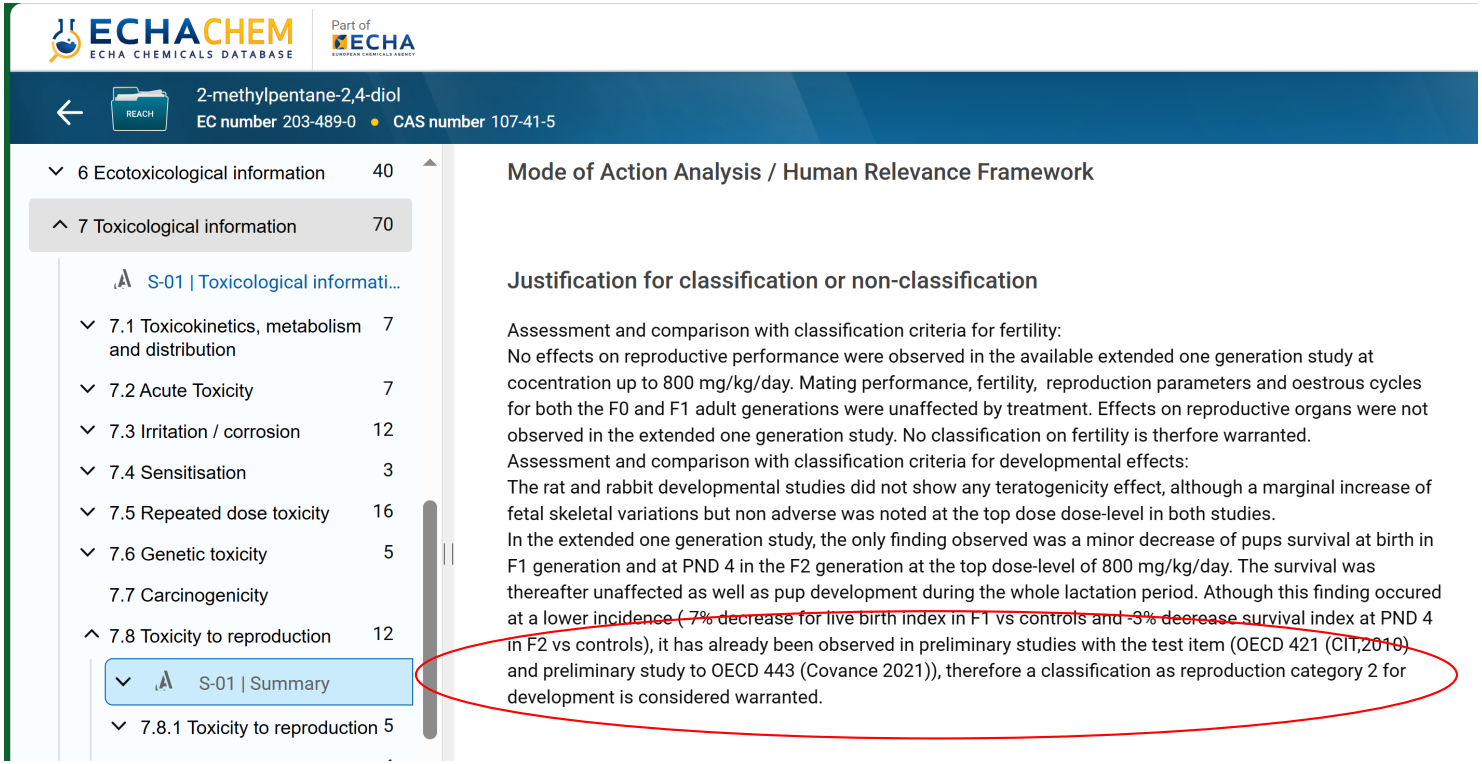
Additional endpoints evaluated	
Bioaccumulation	The eMSCA considers the bioaccumulation potential of BTA as low and thereby not fulfilling the criteria for B or vB according to CLP and REACH Annex XIII.
PBT	The eMSCA considers that the Substance is not PBT based on the low bioaccumulation potential of BTA.
vPvB	The eMSCA considers that the Substance is not vPvB based on the low bioaccumulation potential of BTA.
Reproductive toxicity	The eMSCA considers that the substance fulfils the criteria for classification as reproductive toxicant according to CLP. The available information does not suggest that the adverse effects on development observed in rodents are endocrine-mediated.

See Substance Evaluation Conclusion for Benzotriazole, Template SEV conclusion and report (europa.eu)

Reproductive Toxicity – Hexylene Glycol

- Hexylene glycol
- 2-methylpentane-2,4-diol
- EC# 203-489-0
- CAS# 107-41-5
- Recommended classification: Repro tox, Cat 2 (ECHA)

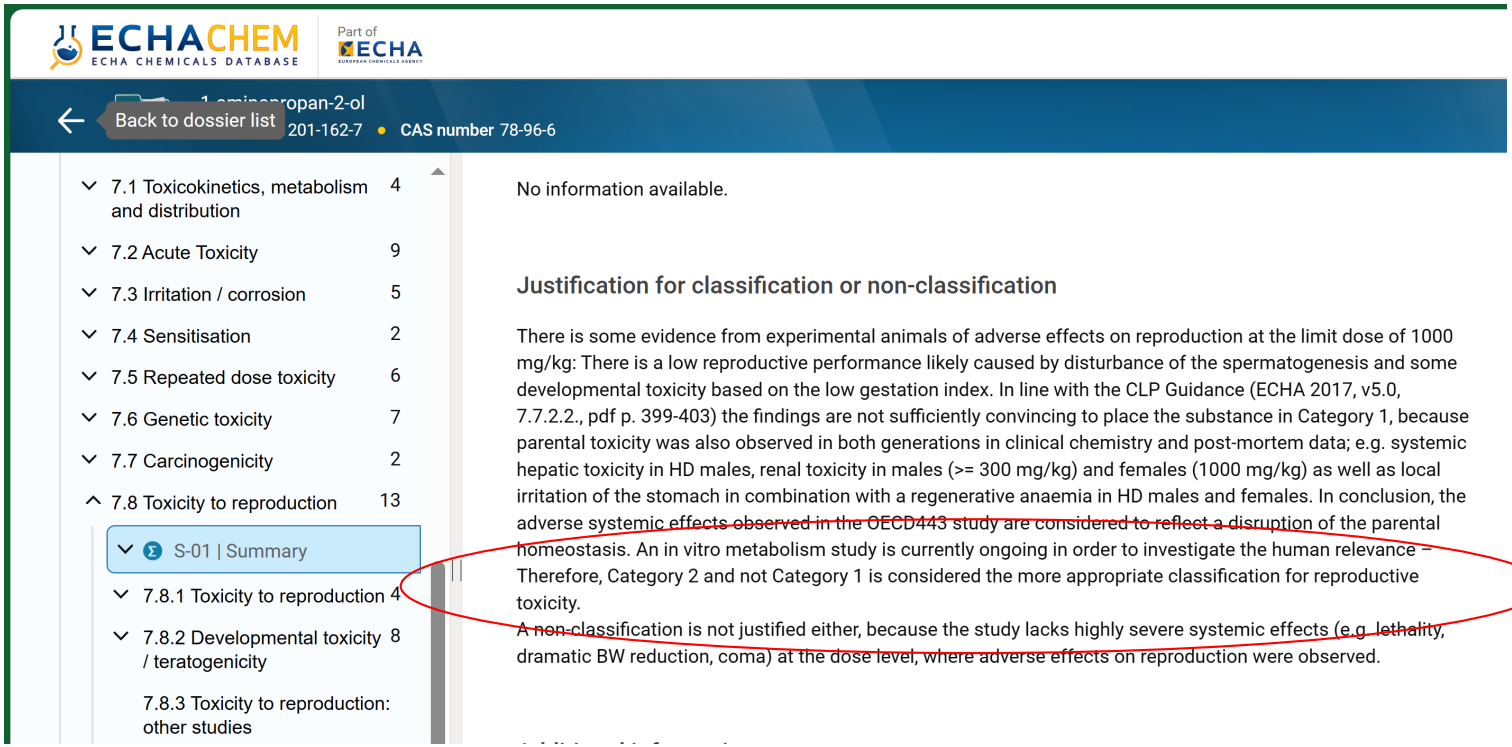
Reproductive Toxicity – Hexylene Glycol



Reproductive Toxicity – Monoisopropanolamine

- Monoisopropanol amine (MIPA)
- 1-aminopropan-2-ol
- EC# 201-162-7
- CAS# 78-96-6
- Possible classification: Repro tox, Cat 2

Reproductive Toxicity – Monoisopropanolamine



Reproductive Toxicity – Hazard Classifications

A.7 REPRODUCTIVE TOXICITY

A.7.1 Definitions and general considerations

A.7.1.1 *Reproductive toxicity* ~~includes~~ refers to adverse effects on sexual function and fertility in adult males and females, as well as ~~*adverse effects on development of the offspring.*~~ ~~D~~developmental toxicity in the offspring, occurring after exposure to a substance or mixture. Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual functionand fertility or to developmental toxicity. Nonetheless, ~~chemicals~~ substances and mixtures with these effects shall be classified as reproductive toxicants.

Reproductive Toxicity – Hazard Classifications

Figure A.7.1(a): Hazard categories for reproductive toxicants

CATEGORY 1:	**Known or presumed human reproductive toxicant** Substance shall be classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
Category 1A:	**Known human reproductive toxicant** The classification of a substance in this category is largely based on evidence from humans.
Category 1B:	**Presumed human reproductive toxicant** The classification of a substance in this category is largely based on evidence from experimental animals. Data from animal studies shall provide sufficient evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.

Reproductive Toxicity – Hazard Classifications

CATEGORY 2: **Suspected human reproductive toxicant**

Substances shall be classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects, and where the evidence is not sufficiently convincing to place the substance in Category 1. For instance, deficiencies in the study may make the quality of evidence less convincing, and in view of this, Category 2 would be the more appropriate classification.

Figure A.7.1(b): Hazard category for effects on or via lactation

EFFECTS ON OR VIA LACTATION

Effects on or via lactation shall be classified in a separate single category. Chemicals that are absorbed by women and have been shown to interfere with lactation or that may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified to indicate this property ~~hazardous to breastfed babies~~. ~~This classification~~ Classification for effects via lactation shall be assigned on the basis of:

(a) absorption, metabolism, distribution and excretion studies that indicate the likelihood the substance would be present in potentially toxic levels in breast milk; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) human evidence indicating a hazard to babies during the lactation period.

Reproductive Toxicity – Hazard Classifications

Table A.7.1: Cut-off values/concentration limits of ingredients of a mixture classified as reproductive toxicants or for effects on or via lactation that trigger classification of the mixture

Ingredients classified as:	Cut-off values/concentration limits triggering classification of a mixture as:		
	Category 1 reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via lactation
Category 1 reproductive toxicant	≥ 0.1%		
Category 2 reproductive toxicant		≥ 0.1 %	
Additional category for effects on or via lactation			≥ 0.1 %

A.7.3.2 Classification of mixtures when data are available for the complete mixture

Available test data for the mixture as a whole may be used for classification on a case-by-case basis. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations and analysis (*e.g.*, statistical analysis, test sensitivity) of reproduction test systems.

Reproductive Toxicity – Hazard Classifications

C.4.10 ~~TOXIC TO~~ REPRODUCTIVE ~~ION~~TOXICITY (CONTINUED)
(Classified in Accordance with Appendix A.7 of this section)
(EFFECTS ON OR VIA LACTATION)

Pictogram
No Pictogram

Hazard category	**Signal word**	**Hazard statement**
No designated number	*No signal word*	May cause harm to breast-fed children

(*See* Table A.7.1 in Appendix A.7)

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Obtain special instructions before use. **Do not breathe dusts or mists.** *- if inhalable particles of dusts or mists may occur during use.* **Avoid contact during pregnancy and while nursing.** **Wash … thoroughly after handling.** …Chemical manufacturer, importer, or distributor to specify parts of the body to be washed after handling. **Do not eat, drink or smoke when using this product.**	**If exposed or concerned: Get medical advice/attention.** Chemical manufacturer, importer, or distributor to select medical advice or attention as appropriate.		

Reproductive Toxicity – Hazard Classifications

C.4.10~~TOXIC TO~~ REPRODUCTIVE ~~ION~~T~~oxicity~~OXICITY
(Classified in Accordance with Appendix A.7 of this section)

Pictogram
Health hazard

Hazard category	**Signal word**	**Hazard statement**
1A and 1B	Danger	May damage fertility or the unborn child <...> <<...>>
2	Warning	Suspected of damaging fertility or the unborn child <...> <<...>>
		< > *(state specific effect if known)*
		<<...>>*(state route of exposure if no other routes of exposure cause the hazard)*

Precautionary statements			
Prevention	**Response**	**Storage**	**Disposal**
Obtain special instructions before use. **Do not handle until all safety precautions havebeen read and understood.** **Wear protective gloves/protective clothing/eye protection/face protection/ . . .** Chemical manufacturer, importer, or distributor to specify ~~type of~~ the appropriate personal protective equipment~~, as required~~.	**If exposed or concerned: Get medical advice/attention.** Chemical manufacturer, importer, or distributor to select medical advice or attention as appropriate.	**Store locked up.**	**Dispose of contents/container to...** ... in accordance with local/regional/national/international regulations (to be specified). Chemical manufacturer, importer, or distributor to specify whether disposal requirements apply to contents, container, or both.

Reproductive Toxicity – How Do We Present?

- Just send an updated SDS directly or through your distributor?
- Meet with key customers, distributors, explaining what they will receive (new SDS, new labels)?
- Industry response explaining raw material test results but, at working MWF dilutions, hazard is greatly reduced (but not zero)?
- All of the above?

Reproductive Toxicity – How Do We Present?

- What do you think?
- Questions?