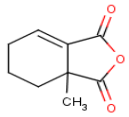
EXECUTIVE SUMMARY

Methyltetrahydrophthalic Anhydride – Oral Risk Assessment - CAS #s 11070-44-3 and 34090-76-1



PARAMETER	LEVEL	UNITS	DERIVED
NOAEL (no-observed-adverse-effect level)	30	mg/kg-day	From a gavage combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test in rats.
Oral RfD* (oral reference dose)	Not identified		
TAC (total allowable concentration)	0.05 (total)**	mg/L	Limited to 0.05 mg/L per NSF/ANSI 61 (2012) Annex A requirements for a qualitative risk assessment, due to the lack of a repeated-dose study of ≥ 90 days.
SPAC (single product allowable concentration)	0.05 (total)**	mg/L	
STEL (short term exposure level)	0.05 (total)**	mg/L	

***** A risk value was derived for comparative purposes only, to ensure that the derived comparative TAC was ≥ 0.05 mg/L, the qualitative level set according to the requirements of NSF/ANSI 60 and 61, Annex A.

** The *total* of methyltetrahydrophthalic anhydride and the four organic anhydride class members (nadic methyl anhydride, tetrahydrophthalic anhydride, hexahydrophthalic anhydride, and methylhexahydrophthalic anhydride) for which it serves as a surrogate.

EXPOSURE SUMMARY	Organic anhydrides are used as epoxy resin hardeners and curing agents, and as chemical intermediates. Most exposure is occupational. Trace amounts may leach from epoxy or alkyd resin components in contact with food or drinking water. However, all such exposure is likely to be to the corresponding acid.
KEY STUDY	A weight-of-evidence review of genetic toxicity and animal studies was used in conformance with NSF/ANSI 61 (2012) Annex A requirements for a qualitative risk assessment. A comparative risk value was derived from a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), as reported in OECD SIDS (Organisation for Economic Co-Operation and Development Screening Information Data Set), 2004. Tetrahydromethyl-1,3-isobenzofuranedione CAS No: 11070-44-3. http://www.inchem.org/documents/sids/sids/11070443.pdf.
CRITICAL EFFECTS	Squamous hyperplasia of the forestomach.
UNCERTAINTY FACTORS	Factors applied in calculating the comparative oral risk value include: • 3x for interspecies extrapolation • 10x for intraspecies extrapolation • 10x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL • 10x for database deficiencies The comparative risk value derived was used for the purpose of comparison with the ≤0.05 mg/L qualitative level (NSF/ANSI 61, 2012: Annex A, Table A4). A total uncertainty factor of 3000x was used to derive the comparative risk value.
TOXICITY SUMMARY	Negative results were obtained in a *Salmonella typhimurium* reverse mutation assay and in a chromosomal aberration assay, suggesting methyltetrahydrophthalic anhydride is not genotoxic. The combined repeated dose toxicity study with the reproduction/developmental toxicity screening test showed forestomach squamous hyperplasia, likely due to the irritant properties of the chemical. There were no statistically significant treatment-related effects on reproduction or developmental parameters, but interpretation of the data was confounded by the small group sizes. Since there is no repeated dose study of at least 90 days duration, the evaluation is limited to the qualitative risk assessment approach under NSF/ANSI 61 (2012) Annex A requirements.
CONCLUSIONS	Based on evaluation of the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, the genetic toxicity data, and the derivation of a comparative TAC (0.07 mg/L) that is greater than the qualitative value (≤ 0.05 mg/L), the action levels derived in this qualitative risk assessment are protective of public health.

EXECUTIVE SUMMARY

Nadic methyl anhydride, Tetrahydrophthalic anhydride, Hexahydrophthalic anhydride, and Methylhexahydrophthalic anhydride – Class-Based Evaluation Level – CAS #s 25143-21-8, 85-43-8, 85-42-7, and 25550-51-0			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	Not identified		-
Oral RfD (oral reference dose)	Not identified		-
TAC (total allowable concentration)	0.05 (total)*	mg/L	From a class-based evaluation using the TAC for methyltetrahydrophthalic anhydride per NSF/ANSI 61 (2012) Annex A requirements
SPAC (single product allowable concentration)	0.05 (total)*	mg/L	From a class-based evaluation using the SPAC for methyltetrahydrophthalic anhydride per NSF/ANSI 61 (2012) Annex A requirements
STEL (short term exposure level)	0.05 (total)*	mg/L	From a class-based evaluation using the STEL for methyltetrahydrophthalic anhydride per NSF/ANSI 61 (2012) Annex A requirements
* The *total* of methyltetrahydrophthalic anhydride and the four organic anhydride class members (nadic methyl anhydride, tetrahydrophthalic anhydride, hexahydrophthalic anhydride, and methylhexahydrophthalic anhydride) for which it serves as a surrogate.			

EXPOSURE SUMMARY	This class of organic anhydrides is used as epoxy resin hardeners and curing agents, and as chemical intermediates. Most exposure is occupational. Trace amounts may leach from epoxy or alkyd resin components in contact with food or drinking water. However, all such exposure is likely to be to the corresponding acid.
NEED FOR CLASS-BASED CRITERIA	The need for nadic methyl anhydride action levels prompted the need for establishment of the class. Since nadic methyl anhydride has no toxicological information relevant to establishing an oral RfD, use of one or more surrogate chemicals was warranted.
ESTABLISHMENT OF THE CLASS	This class was established by the U.S. EPA under the High Production Volume (HPV) chemicals program. The four anhydrides comprising this class (nadic methyl anhydride, tetrahydrophthalic anhydride, hexahydrophthalic anhydride, and methylhexahydrophthalic anhydride) are closely related by structure, physical properties, and toxicity when compared with the surrogate chemical for the class, methyltetrahydrophthalic anhydride.
REVIEW OF CHEMICAL CLASS TOXICITY INFORMATION	The available toxicity information for this chemical class has been reviewed in Sections 6-8 of this document. Included are: acute toxicity studies, guideline reverse mutation and chromosomal aberration assays for several class members, and a combined repeated dose toxicity study with reproduction/developmental toxicity screening for methyltetrahydrophthalic anhydride. Negative results were obtained in all the available genetic toxicity studies. The repeated dose/reproduction and developmental screening study showed forestomach squamous hyperplasia, likely due to the irritant properties of the chemical, and no obvious treatment-related effects on reproduction or development, although group sizes were small. Since there is no repeated dose study of at least 90 days duration for any member of the class or for the surrogate chemical, evaluation is limited to the qualitative risk assessment approach under NSF/ANSI 61 (2012) Annex A requirements.
CLASS-BASED EVALUATION CRITERIA	The class-based evaluation criteria are 0.05 mg/L total for the TAC, SPAC, and STEL based on the available toxicity data for the surrogate chemical, methyltetrahydrophthalic anhydride.
CONCLUSIONS	Based on evaluation of all toxicity information available for this class of organic anhydrides, the action levels derived in this qualitative risk assessment are protective of public health.