

Draft 2010 03 23

## Available studies and testing proposal for Melamine registration Annex VII and VIII

### 1 Summary

An overview of the available studies for each endpoint under the Annexes VII and VIII under REACH is presented together with a classification into relevance and reliability.

Most of the endpoints of Annex VII and VIII of REACH are covered by existing data or by waivers. Only one study needs to be performed, i.e.

8.3 Sensitization. First a Local Lymph Node Assay was proposed according to REACH, but due to dissolution problems now a Guinea Pig Maximisation Test is performed. The test is ongoing.

### 2 Introduction

A testing strategy was proposed on 1 December 2009 to the melamine consortium to comply with the requirements posed in Annexes VII and VIII of REACH and to enable a registration of melamine timely before 1 December 2010. This proposal was discussed with the lead registrant.

Now, after obtaining additional data and after input of them into IUCLID a retrospective data gap analysis and test proposal is presented. This is to provide an overview on the available data and the waiving methods for the individual endpoints.

Below, the available studies and publications are now classified according to their usefulness for REACH (key study - study of a weight of evidence approach - supporting study) and to their reliability (Klimisch scores).

A proposal to cover the requirements of Annexes IX and X will be presented later.

#### Abbreviations used:

Key: key study  
WoE: weight of evidence study  
Supp: supporting study

Reliability: the number after the year of the study is the allocated Klimisch score for reliability (e.g. Reuse 2009 /2)

### 3 Updated data gap analysis and test proposals - retrospective, after input of all available data into IUCLID

The numbering system is that used in the REACH annexes.

REACH Endpoint	Study / Waiver
<b>7. Physical-chemical endpoints</b>	-
7.1. State of the substance at 20°C and 101,3 kPa	WoE: Reuse 2009 /2 (Report for Borealis), Ullmann 2006 /4 (handbook) Supp: SDS of Borealis /4, Cytec /4, Pulawny /4
7.2. Melting / freezing point	Key: Reuse 2009 /2 (Report for Borealis) Supp: Ullmann 2006 /4 (handbook); Gmelin /4 (handbook); BASF 1999 /4.
7.3. Boiling point	Key: Waiver. Supp: QSAR 2009 /2, NTP 2009 /4 (Publication).  A waiver is proposed based on the melting point of >300 °C and decomposition. Justification according to REACH: "The study does not need to be conducted: – for solids which either melt above 300°C or decompose before boiling. In such cases the boiling point under reduced pressure may be estimated or measured".
7.4. Relative density	Key: Reuse 2009 /2 (Report for Borealis) Supp: Ullmann 2006 /4, Gmelin /4, 2 x BASF 1999 /4 (SDS).
7.5. Vapour pressure	Key: Waiver Supp: Hirt 1960 /2 (Publication), QSAR 2009 /2; Ullmann 2006 /4; Woll 1993 /4 (BASF report).  A waiver is proposed based on the melting point of >300 °C. Justification according to REACH: "The study does not need to be conducted if the melting point is above 300°C".
7.6. Surface tension	Key: Waiver.  A waiver is proposed based on the chemical structure and the purpose of melamine. Melamine has not both polar and unpolar groups, which are considered to be necessary for surfactant properties (from the guidance document). Surface activity is not a desired property of melamine. Justification according to REACH: "The study need only be conducted if: – based on structure, surface activity is expected or can be predicted; or – surface activity is a desired property of the material
7.7. Water solubility	Key: Reuse 2009 /2 (Report for Borealis) Supp: Ullmann 2006 /4, Gmelin /4, BASF 1999 /3 (SDS), Walz 1991 /4 (BASF report).
7.8. Partition coefficient n-	Key: Junghans 2009 /2 (Report for Borealis)

REACH Endpoint	Study / Waiver
octanol/water	Supp: Brunner 1988 /4 (BASF report)
7.9. Flash-point	Key: Waiver Supp: Gestis 2009 /3 (Databank), DSM 1996 /3 (SDS)  A waiver is proposed based on the physical state of melamine. The flash point is a possible characteristic of liquids and not of solids. The test procedure A.9 is applicable to liquid substances. Melamine is a solid with a melting temperature >300 °C. None of the waiving criteria according to REACH apply.
7.10. Flammability	Key: Reuse 2009 /2 (Report for Borealis) Supp: BASF 1987 /3 (short report)
7.11. Explosive properties	Key: Waiver [Supp, on dust explosivity: Gresslehner 2008 /2 (report for Borealis), Rainbauer 1989 /4 (report for Borealis)]  A waiver is proposed based on the chemical structure of melamine. Melamine does not contain groups associated with explosive properties, as they are listed in the ECHA "Guidance on information requirements and chemical safety assessment" or the ECHA "Guidance on the Application of the CLP Criteria".
7.12. Self-ignition temperature	Key: Reuse 2009 /2 (Report for Borealis) Supp: DSM 1996 /3 (SDS), BASF 1987 /4 (report)
7.13. Oxidising properties	Key: Waiver. Supp: Reuse 2009 /4 (Report for Borealis), BASF 1999 /4 (short report).  REACH criterion for waiving: The study does not need to be conducted if: ... the substance is incapable of reacting exothermically with combustible materials, for example on the basis of the chemical structure (e.g. organic substances not containing oxygen or halogen atoms and ...). CLP criteria: For organic substances or mixtures the classification procedure for this class shall not apply if: (a) the substance or mixture does not contain oxygen, fluorine or chlorine; or (b) ... Melamine does not contain oxygen or halogen atoms.
7.14. Granulometry	Key: Synlab 2008 /2 (Report for Borealis) Supp: Gresslehner 2008 /4 (Report for Borealis), BASF-DSM-CL 2005 /4 (BASF report), Pulawny 2009 /4, 2x Reiner 2007 (BASF), Rich 2010 /4 (Cytec).
<b>8. Toxicity</b>	-
8.1. Skin irritation or skin corrosion	Key: Rijcken 1995 /1 (report for DSM) Supp: Hofmann 1969 /4 (BASF report), Shaffer 1955 /4 (Cytec report), Fassett 1981 /3 (unknown).
8.2. Eye irritation	WoE: Hofmann 1969 /4 (BASF report) Supp: Shaffer 1955 /4 (Cytec report), Marhold 1972 /3 (publication)
8.3. Skin sensitization	Key: The performance of a new test was proposed. A test

REACH Endpoint	Study / Waiver
<p>Steps: (1) an assessment of the available human, animal and alternative data, (2) <i>In vivo</i> testing.</p>	<p>was recently ordered by DSM. Supp: Hollander 1940 /3 (Cytec report), Fassett 1981 /3 (unknown).  Comments: Data obtained from Cytec: The available letters and raw data on a human patch study performed in 1940 point to a study that was performed with 208 volunteers. 207/208 turned out to be negative. One was positive. The sensitizing potential of the used Elastoplast patch itself was obvious - and could have interfered with the action of melamine. The method is not (sufficiently) described and can therefore not be compared to actual standard methods. No characterisation of the used substance melamine is available.</p>
<p>8.4. Mutagenicity</p>	<p>-</p>
<p>8.4.1. <i>In vitro</i> gene mutation study in bacteria</p>	<p>Key: Finch 1981 /2 (Cytec report). Supp: Litton 1977 /2 (DSM report), Haworth 1981 /2 (publication), Kubo 2002 /2 (publication), Seiler 1973 /4 (publication), Ishiwata 1991 /4 (publication)</p>
<p>8.4.2. <i>In vitro</i> cytogenicity study in mammalian cells or <i>in vitro</i> micronucleus study</p>	<p>Key: Galloway 1987 /2 (Publication).</p>
<p>8.4.3. <i>In vitro</i> gene mutation study in mammalian cells, if a negative result in Annex VII, section 8.4.1. and Annex VIII, section 8.4.2.</p>	<p>Key: Finch 1981 /2 (Cytec report). Supp: McGregor 1988 /2 (Publication),</p>
<p>8.4.4 <i>In vivo</i> mutagenicity studies. Appropriate <i>in vivo</i> mutagenicity studies shall be considered in case of a positive result in any of the genotoxicity studies in Annex VII or VIII.</p>	<p>Key: A waiver is formulated for formal reasons, although plenty of studies are available. Melamine is not mutagenic, demonstrated by a series of studies, according to Annex VII and VIII.</p>
<p>8.5. Acute toxicity</p>	<p>-</p>
<p>8.5.1. By oral route</p>	<p>Key: NTP 1983 /2 (Publication). Supp: Hofmann 1969 /4 (BASF), Hoechst 1963 /4, Shaffer 1995 /4 (Cytec).</p>
<p>8.5.2. By inhalation</p>	<p>Key: Muijser 1998 /1 (report for DSM) Supp: Hofmann 1969 /3 (BASF), Ubaydullayev 1993 /3 (publication).</p>
<p>8.5.3. By dermal route</p>	<p>Key: waiver. Supp: Shaffer 1995 /4 (Cytec).  REACH criterion for waiving: "Testing for acute toxicity by the dermal route is appropriate if: (1) inhalation of the substance is unlikely; and (2) skin contact in production and/or use is likely; and (3) the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin." Criteria (1) and (3) are not fulfilled, therefore testing is not appropriate. REACH, Annex VII and VIII, requires acute toxicity studies with 2 routes of applications</p>

REACH Endpoint	Study / Waiver
<p>8.6. Repeated dose toxicity</p> <p>8.6.1. Short-term repeated dose toxicity study.</p> <p>8.6.2. Sub-chronic toxicity study</p>	<p>8.6.1 or 8.6.2 can be chosen.</p> <p>Oral route: Key: NTP 1983 /2 (Publication). Supp: Hard 2009 /2 (Publication), Reno 1983 /1 (Cytec report), Tyl 1982 und Heck1985 /1 (Cytec report + Publication), 2 x Shaffer 1955 /3 (Cytec report), Lipschitz 1945 /3 (Publication).</p> <p>Inhalation route: Key: waiver. Waiver: A rapid and complete absorption was found after the oral route. The same can be assumed as a worst case for the inhalation route. The absorbed doses can be calculated according to the Guidance Document on Information requirement and CSA, Table R.8. Melamine is not irritative to eyes and skin, and it can be expected therefore that no local but mainly systemic toxic effects would occur (if any). There is apparently no metabolism of melamine in the organism and by this no first pass effect. It is therefore justified to estimate the possible toxic effects after inhalation exposure, based on the outcome of the oral experiments. The NOAEL<sub>Inhalation</sub> can be estimated from the NOAEL<sub>Oral</sub> taking into account the respiratory volume. This is sufficient for a risk assessment, and does not justify an own inhalation animal experiment.</p> <p>Dermal route: Key: waiver. Waiver: A low dermal absorption was estimated for melamine, whereas a rapid and complete absorption was found after the oral route. It can therefore be derived that the orally absorbed dose will be higher than the dermally absorbed dose (at comparable external doses). There is apparently no metabolism of melamine in the organism and by this no first pass effect. Due to the absence of a metabolism, a similar behaviour of melamine is predictable following systemic absorption, independent of the route of exposure. It is therefore justified to compare the possible toxic effects of the absorbed doses after oral and dermal exposure. The toxic effects (if any) after the same external doses will therefore be much higher at the oral route than at the dermal one. The NOAEL<sub>Oral</sub> can be considered as the worst case for the not determined NOAEL<sub>dermal</sub>. This is sufficient for a classification and a risk assessment, and does not justify an own dermal animal experiment. Supp: Ubaydullayev 1993 /3 (publication)</p>
<p>8.7. Reproductive toxicity</p> <p>8.7.1. Screening for reproductive/developmental toxicity.</p>	<p>8.7.1. Key: waiver, only for Annex VII and VIII purposes. Supp: NTP 1983 /2 (publication), Ubaydullayev 1993 /3 (publication).</p> <p>REACH criterion for waiver: "This study does not need to be conducted if: – a pre-natal developmental toxicity study (Annex IX,</p>

REACH Endpoint	Study / Waiver
8.7.2 Pre-natal developmental toxicity study, one species.	8.7.2) or a two-generation reproductive toxicity study (Annex IX, section 8.7.3) is available."  8.7.2 Key: Hellwig 1996 /2 (BASF report) Supp: Thiersch 1957 /3 (Publication)
8.8. Toxicokinetics 8.8.1. Assessment of the toxicokinetic behaviour of the substance to the extent that can be derived from the relevant available information	WoE: Mast 1983 /2 (Publication), Sugita /2 1991 (Publication), Liu 2010 /2 (Publication), Yang 2009 /2 (Publication), Baynes 2008 /2 (Publication). Supp: Lipschitz 1945 & 1944 /3 (Publication), Worzalla 1974 /2 (Publication).
<b>9. Ecotoxicity</b>	-
9.1. Aquatic toxicity	-
9.1.1. Short-term toxicity testing on invertebrates (preferred species <i>Daphnia</i> )	Key: Frazier 1988 /1 (Report for Cytec) Supp: Adema 1978 /2 (Report for DSM).
9.1.2. Growth inhibition study aquatic plants (algae preferred)	Key: Drzdowski 1988 /2 (Report for Cytec) Supp: Oldersma 1982 /2 (Report for DSM)
9.1.3. Short-term toxicity testing on fish: The registrant may consider long-term toxicity testing instead of short-term.	WoE: Goodrich 1984 /2 (Cytec Report). Supp: Vaessen 1982 /4 (DSM Report), Pagga 1979 /4 (BASF report), Nite 2010 /2 (Publication), Jansen 1978 /4 (DSM report)
9.1.4. Activated sludge respiration inhibition testing	WoE: Pagga 1979 /4 (BASF reports), Hockenbury 1977 /4 (Publication) Supp: Tillmann 1990 /4 (BASF report).
9.2. Degradation 9.2.1. Biotic	-
9.2.1.1. Ready biodegradability	WoE: Nite 2010 /2 (Publication), Taeger 1983&1982 /2 (BASF report), Pagga 1991 /4 (BASF reports) Supp: Fimberger 1997 /4 (Publication), Niemi 1987 /4 (Publication), Swope 1950 /4 (Publication).
9.2.2 Abiotic 9.2.2.1 Hydrolysis	WoE: Gmelin 1971 /4 (handbook), Ullmann 2006 /4 (handbook).
9.3. Fate and behaviour in the environment	-
9.3.1. Adsorption / desorption screening	Key: waiver. Supp: QSAR 2009 /2, ECETOC 1983 /3 (Publication).  REACH criterion for waiving: "The study does not need to be conducted if: – based on the physicochemical properties the substance can be expected to have a low potential for adsorption (e.g. the substance has a low octanol water partition coefficient);..."



ECETOC (1983). Melamine. Joint Assessment of Commodity Chemicals; European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC). Report no.: JACC 001 Melamine. Owner company: ECETOC.

EPA (1992). Dermal exposure assessment: principles and applications. EPA Interim Report. [http://www.epa.gov/oppt/exposure/presentations/efast/usepa\\_1992d\\_dermalea.pdf](http://www.epa.gov/oppt/exposure/presentations/efast/usepa_1992d_dermalea.pdf). Report no.: EPA/600/8-91/011B. Owner company: EPA.

EPA (2009a). Estimation of the adsorption coefficient of melamine. KOCWIN v2.00 within EPA EpiSuite 4.0. Testing laboratory: Seibersdorf Labor GmbH, 2444 Seibersdorf, Austria. Report date: 2009-11-25.

EPA (2009b). Estimation of the Henry-constant of melamine. HENRYWin v3.20 within EPA EpiSuite 4.0. Testing laboratory: Seibersdorf Labor GmbH, 2444 Seibersdorf, Austria. Report date: 2009-11-25.

EPA (2010). Estimation of the permeation coefficient of melamine. DermWin v1.43, as part of EpiSuite 4.0, provided by the US EPA. Testing laboratory: Seibersdorf Labor GmbH, A-2444 Seibersdorf, Austria. Report date: 2010-02-17.

Elmore E, Fitzgerald MP (1990). Evaluation of the Bioluminescence Assays as Screens for Genotoxic Chemicals. *Mutation and the Environment, Part D*, pp. 379-387.

Fassett DW and Roudabush RL (1981). Unknown. *Lab. Ind. Med.*, Eastman Kodak Co., unpubl. observations; cited i. a. in ECB IUCLID4 2009.

Fimberger EA (1997). Bestimmung von Neben- und Abbauprodukten des Melamins mittels Kapillarelektrophorese und Abbauverhalten des Melamins in Kläranlagen. Translation: "Determination....", see below. Diplomarbeit zur Erlangung des Magistergrades an der Naturwissenschaftlichen Fakultät der Universität Salzburg, Austria. Report date: 1997-07-10.

Finch RA (1981a). Determination of the mutagenic potential of melamine using the plate incorporation method of the Ames Salmonella/microsome mutagenicity test. Testing laboratory: Raltech Scientific Services. Report no.: 81560. Owner company: American Cyanamid Co. Report date: 1981-09-14.

Finch RA (1981b). Determination of the mutagenic potential of melamine using the CHO/HGPRT Chinese hamster ovary cell forward mutation assay. Testing laboratory: Raltech Scientific Services. Report no.: 81552. Owner company: American Cyanamid Co. Report date: 1981-09-14.

Finch RA (1981c). Determination of the DNA-damaging potential of melamine using the in vitro Chinese hamster ovary cell Sister Chromatid Exchange assay. Testing laboratory: Raltech Scientific Services. Report no.: 81553. Owner company: American Cyanamid Co. Report date: 1981-10-15.

Fouremant P, Mason JM, Valencia R, Zimmering S. (1994). Chemical mutagenesis testing in *Drosophila*. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environmental and molec. Mutagenesis* 23(3), 208-227, 1994; cited in ECB IUCLID4 2009.

Frazier S (1988). Acute Toxicity of CT-338-87 to *Daphnia Magna*. Unpublished report. Furthermore: a personal mail of 18 November 2009 on some details of the study. Testing laboratory: Analytical Bio-Chemistry Laboratories, Inc. Report no.: 36645. Owner company: American Cyanamid Company. Report date: 1988-01-15.

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluation of 108 chemicals. *Environ. Mol. Mutagen.*, 10(Suppl.10), 1-175, (1987).

Gestis (2009). Gestis Stoffdatenbank (German data bank for substances). <http://www.dguv.de/bgja/de/gestis/stoffdb/index.jsp>.

Gmelin (1971). *Gmelins Handbuch der Anorganischen Chemie*. Gmelins Handbuch der Anorganischen Chemie, 14 Kohlenstoff, Teil D1, page 361.

Gold LS, Slone TH, Bernstein L (1989). Summary of Carcinogenic Potency and Positivity for 492 Rodent Carcinogens in the Carcinogenic Potency Database. *Environ. Health Perspect.* 79, 259-272, 1989.

Goodrich, Lech J (1984). Acute and subacute toxicity to rainbow trout. Unpublished report. Testing laboratory: Wisconsin's aquatic laboratory at Great Lakes Research Facility. Owner company: American Cyanamid Co. Study number: 85-21.

Gresslehner G. (2008). Explosionsschutz - Melamin- und Harnstoffstäube - Auswertung und Diskussion der Untersuchungsergebnisse (Protection against explosion - melamine and urea dust - Evaluation and discussion of results). Testing laboratory: Synex. Report no.: G07-070S. Owner company: Agrolinz Melamin International. Report date: 2008-04-25.

Hard GC, Flake GP, Sills RC (2009). Re-evaluation of kidney histopathology from 13-week toxicity and two-year carcinogenicity studies of melamine in the F344 rat: morphologic evidence of retrograde nephropathy. *Vet Pathol* 46, pp 1248-1257.

Hauck RD, Stephenson HF (1964). Nitrification of Triazine Nitrogen. *Journal of agricultural and food chemistry*, 12, 147-151.

Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E (1983). Salmonella mutagenicity test results for 250 chemicals. *Environmental Mutagenesis Supplement 1*: 3-142 (1983). Testing laboratory: Case Western Reserve University (CWR) and 2 others.

Hazelton (1953). Melamine. Chronic feeding - rats. Final report. Testing laboratory: Hazelton Laboratories, Virginia. Owner company: American Cyanamid Co. Report date: 1953-11-27.

Heck HD'A, Tyl RW (1985). The induction of bladder stones by terephthalic acid, dimethyl terephthalate and melamine (2,4,6-Triamino-s-triazine) and its relevance to risk assessment. *Regul. Toxicol. Pharmacol.*, 5, 294-313, (1985).

Hellwig J (1996). Melamine - Prenatal Toxicity in Wistar Rats after oral Administration (Diet). unpublished report. Testing laboratory: BASF AG, Department of Toxicology. Study number: 32R0242/94007. Report date: 1996-04-15.

Hockenbury MR, Grady CPL (1977). Inhibition of nitrification-effects of selected organic compounds. *Journal WPCF* 49(1), 768-777; cited in ECB IUCLID4 2009.

Hoechst (1963). Unknown. Unpublished report; cited in ECB IUCLID4 2009. Report no.: 63.0065. Owner company: Hoechst AG, Cassella AG Frankfurt/Main. Report date: 1963-07-05.

Hofmann (1969). Gewerbetoxikologische Vorprüfung (Occupational toxicology screening). Unpublished report. Testing laboratory: BASF AG, Department of Toxicology. Report no.: XIX/5. Owner company: BASF. Report date: 1969-04-23.

Hollander L (1940). Human patch test. A series of letters and protocols of 1940. Testing laboratory: Pittsburgh skin and cancer foundation. Owner company: American Cyanamid Co.

Ishiwata H et al. (1991). *J. Food Hyg. Soc. Japan*, 32, 408-413, (1991); cited in ECB IUCLID4 2009.

Jansen B (1978). Unknown. Cited in ECETOC: Joint Assessment of Commodity Chemicals, No.1, Melamine, Brussels, 1983. Owner company: DSM.

Jansen B (1982). Onderzoek naar de fycotoxiteit van Melafsliek t. b. v. landbouwkundige toepassingen. Testing laboratory: DSM. Report no.: CRO MK 82 359 MR-1. Owner company: DSM. Report date: 1982-03-22.

Koch A (1986). Onderzoek naar het effect van melamine in grondpercolaat op de wortelont-wikkeling van kiemplanten (Investigation of the effects of melamine in groundwater on the development of sliver-wort seedlings). Testing laboratory: DSM Research. Report no.: Res MK 86 769 BO-MVR. Owner company: DSM. Report date: 1986-06-20.

- Kubo T, Urano K, Utsumi H. (2002). Mutagenicity Characteristics of 255 Environmental Chemicals. *J. Health Science*, Vol. 48(6), 545-554, 2002.
- Lech JJ, Szmania DC (1984a). Uptake, Elimination and Bioaccumulation of Melamine in Fathead Minnows. Testing laboratory: Medical College of Wisconsin, Department of Pharmacology & Toxicology, Milwaukee, Wisconsin, USA. Owner company: American Cyanamid Company. Study number: 05-01.
- Lech JJ, Szmania DC (1984b). Uptake, Elimination and Bioaccumulation of Melamine in Rainbow Trout. Testing laboratory: Medical College of Wisconsin, Department of Pharmacology & Toxicology, Milwaukee, Wisconsin, USA. Owner company: American Cyanamid Company. Study number: 85-13.
- Lipschitz WL, Hadidian Z (1944). Amides, amines and related compounds as diuretics. *J. Pharm. Exp. Ther.* 81 (1944), 84-94.
- Lipschitz WL, Stokey E (1945). The mode of action of three new diuretics: Melamine, Adenine and Formoguanamine. *J. Pharmacol. Exp. Ther.*, 83, 235-249, (1945).
- Litton Bionetics Inc. (1977). Mutagenicity evaluation of melamine (2,4,6-triamine-s-triazine). Testing laboratory: Litton Bionetics Inc. Report no.: 2838. Owner company: DSM Research and patents, Geleen, Holland.
- Liu G, Li S, Jia J, Yu C, He J, Yu C and Zhu J (2010). Pharmacokinetic study of melamine in rhesus monkey after a single oral administration of a tolerable daily intake dose. *Regulatory Toxicology and Pharmacology* 56(2) (2010) 193-196. Testing laboratory: Shanghai Xuhui Central Hospital, Shanghai University of Chinese Traditional Medicine, Center for Clinical Laboratory Development, Chinese Academy of Medicine Science, Beijing.
- Lüers H, Röhrborn G (1963). The mutagenic activity of Ethyleneimino derivatives with different numbers of reactive groups. *Genet. Today Proc. Int. Congr.* 11th, 1, abstract, 64-65.
- Marhold JV (1972). Sbornik vysledku toxikologickeho vysetreni latek a pripravku. *Chemickeho Prumyclu*, Vol. ?, 153, 1972; cited in RTECS; cited in ECB IUCLID4 2009. Testing laboratory: Institut Pro Vychovu Vedoucich Pracovniku, Praha, Czechoslovakia.
- Mast RW, Jeffcoat AR, Sadler BM, Kraska RC, Friedman MA (1983). Metabolism, disposition and excretion of [<sup>14</sup>C]Melamine in male Fischer 344 Rats. *Fd Chem. Toxic.*, Vol. 21, No. 6, pp 807-810.
- Mast RW, Friedman MA, Finch RA (1982). Mutagenicity testing of melamine. *Toxicologist* 2, 172, (1982).
- Mast RW, Naismith RW, Friedman MA, (1982). Mouse Micronucleus Assay of Melamine. *Environ. Mutagenesis* 4, pp. 340-341.
- Matsui-Yuasa I. et al. (1992). Spermidine/spermine N-acetyltransferase, a new biochemical marker for epithelial proliferation in rat bladder. *Jpn. J. Cancer Res.*, 83, 1037-1040, (1992).
- McGregor DB, Brown A, Cattanch P, Edwards I, McBride D, Riach C, Caspary W (1988). Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay: III. 72 Coded Chemicals. *Environ. Mol. Mutagen.*, 12, 85-154, (1988).
- Melnick RL, Boorman GA, Haseman JK, Montali RJ, Huff J (1984). Urolithiasis and Bladder Carcinogenicity of Melamine in Rodents. *Tox Applied Pharmacol* 72, 292-303. Testing laboratory: National Toxicology Program and Litton Bionetics, USA.
- Mirsalis J, Tyson k, Beck J, Loh F, Steinmetz K, Contreras C, Austere L, Martin S, Spalding J (1983). Induction of unscheduled DNA synthesis (UDS) in hepatocytes following in vitro and in vivo treatment. *Environ. Mutagen.*, 5, 482, (1983).
- Mori S. et al. (2000). *J. Toxicol. Pathol.*, Vol. 13, 93-95, 2000; cited in ECB IUCLID4 2009.

Muijser H (1998). Acute (4-hour) inhalation toxicity study with Melamine in rats. Testing laboratory: TNO Nutrition and Food Research Institute, Toxicology Division. Report no.: V98.420. Owner company: DSM N. V. Heerlen, The Netherlands. Study number: 480001/002. Report date: 1998-04-15.

NITE (2010). Chemical Risk Information Platform (CHRIP). National Institute of Technology and Evaluation. Chemical Risk Information Platform (CHRIP). <http://www.safe.nite.go.jp> and [http://www.safe.nite.go.jp/data/hazkizon/pk\\_e\\_kizon\\_disp.html?k\\_no=0063](http://www.safe.nite.go.jp/data/hazkizon/pk_e_kizon_disp.html?k_no=0063). Report no.: MITI No. 5-1024. Owner company: NITE.

NTP (1981). Salmonella: study summary. Salmonella: study details. Testing status of agents at NTP: <http://ntp.niehs.nih.gov/?objectid=BCC5098D-123F-7908-7B43CE973646AAC4>; and database: [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch). Report no.: 986479. Owner company: National Toxicology Program, USA.

NTP (1982). In vitro cytogenetics - sister chromatid exchanges. Testing status of agents at NTP: <http://ntp.niehs.nih.gov/?objectid=BCC5098D-123F-7908-7B43CE973646AAC4>; and database: [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch). Search results & search term = 108-78-1. Testing laboratory: Litton Bionetics Inc. Report no.: 828756 (Study No. Owner company: National Toxicology Program, USA.

NTP (1983). Carcinogenesis Bioassay of Melamine (CAS No. 108-78-1) in F344/N Rats and B6C3F1 Mice (Feed Study). NIH Publication No. 83-2501. Testing laboratory: Litton Bionetics Inc.; Tracor Jitco Inc.; National Toxicology Program. Report no.: NTP Technical Report Series No. 245. Owner company: US Department of Health and Human Services. National Institute of Health.

NTP (1987). Mouse Lymphoma Study Details. Testing status of agents at NTP: <http://ntp.niehs.nih.gov/?objectid=BCC5098D-123F-7908-7B43CE973646AAC4>; and database: [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch). Search results & search term = 108-78-1. Owner company: National Toxicology Program, USA. Study number: 091419.

NTP (1988). In vivo cytogenetics - sister chromatid exchanges. Testing status of agents at NTP: <http://ntp.niehs.nih.gov/?objectid=BCC5098D-123F-7908-7B43CE973646AAC4>; and database: [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch). Search results & search term = 108-78-1. Owner company: National Toxicology Program, USA. Study number: 951364.

NTP (1989a). In vivo cytogenetics - chromosome aberrations. Testing status of agents at NTP: <http://ntp.niehs.nih.gov/?objectid=BCC5098D-123F-7908-7B43CE973646AAC4>; and database: [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch). Search results & search term = 108-78-1. Owner company: National Toxicology Program, USA. Study number: 951364.

NTP (1989b). Micronucleus - Peripheral blood, bone marrow. Testing status of agents at NTP: <http://ntp.niehs.nih.gov/?objectid=BCC5098D-123F-7908-7B43CE973646AAC4>; and database: [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch). Search results & search term = 108-78-1. Owner company: National Toxicology Program, USA. Study number: 039087.

NTP (1994). Drosophila sex-linked recessive lethal study details. Testing status of agents at NTP: <http://ntp.niehs.nih.gov/?objectid=BCC5098D-123F-7908-7B43CE973646AAC4>; and database: [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch). Search results & search term = 108-78-1. Owner company: National Toxicology Program, USA. Study number: 206373.

NTP (2009). Testing status of agents at NTP. <http://ntp.niehs.nih.gov/index.cfm?objectid=E87C191B-BDB5-82F8-F94BB482E55FD29E>.

Naismith RW (1982). Rat hepatocyte primary culture / DNA repair test. Testing laboratory: Pharmakon Research International Inc. Report no.: PH 311-AC-002-82. Owner company: American Cyanamid Co. Report date: 1982-04-15.

Niemi GJJ, Veith GD, Regal RR, Vaischnav DD (1987). Structural features associated with persistent and degradable chemicals. *Environmental Toxicology And Chemistry* 6, 515-527; cited in ECB IUCLID

4 2009.

Nishihara T, Nishikawa J, Kanayama T, Dakeyama F, Saito K, Imagawa M, Takatori S, Kitagawa Y, Hori S, Utsumi H (2000). Estrogenic Activities of 517 Chemicals by Yeast Two-Hybrid Assay. *J. Health Sci.*, Vol. 46(4), 282-298, 2000.

Nishikawa J. et al. (1998). *Jpn. J. Toxicol. Environ. Health*, Vol. 44, P-32, 1998; cited in Nishihara T. et al., *J. Health Sci.*, Vol. 46(4), 282-298, 2000.

Ogasawara H, Imaida K, Ishiwata H, Toyoda K, Kawanishi T, Uneyama C, Hayashi S, Takahashi M, Hayashi Y (1995). Urinary bladder carcinogenesis induced by melamine in F344 male rats: correlation between carcinogenicity and urolith formation. *Carcinogenesis*, 16, 2773-2777, (1995). Testing laboratory: Division of Pathology and Food Additives. National Institute of Health Sciences, Tokyo.

Okumura M, Hasegawa R, Shirai T, Ito M, Yamada S, Fukushima S (1992). Relationship between calculus formation and carcinogenesis in the urinary bladder of rats administered the non-genotoxic agents, thymine or melamine. *Carcinogenesis*, 13, 1043-1045, (1992). Testing laboratory: First Department of Pathology. Nagoya City University Medical School.

Oldersma H, Hanstveit AO (1982). The effect of the product melamine on the growth of the green alga *Scenedesmus pannonicus*. Testing laboratory: TNO Central Laboratory. Report no.: 81/188. Owner company: DSM / Geleen. Report date: 1982-01-06.

Pagga (1979a). Goldorfentest (Test with *Leuciscus idus*). Testing laboratory: BASF AG. Owner company: BASF AG. Study number: PF12.

Pagga (1979b). Atmungshemmtest mit Belebtschlamm (Kurzzeitatmungstest). Respiration inhibition test (short term respiration test). Testing laboratory: BASF AG, Ökologielabor. Report no.: Öko-Nr 1910405. Owner company: BASF AG. Report date: 1991-06-03.

Pagga (1991). Zahn-Wellens-Test. Testing laboratory: BASF AG Ökologielabor. Report no.: Project No. 1/91/0405/10/1. Owner company: BASF AG. Report date: 1991-03-07.

Perrella FW, Boutwell RK (1983). Triethylenmelamine: An initiator of two-stage carcinogenesis in mouse skin which lacks the potential of a complete carcinogen. *Cancer Letters*, 21, 37-41, (1983).

Philips FS and Thiersch JB (1950). The nitrogen mustard-like action of 2,4,6-tris(ethylen-imino) -s-triazine and other bis(ethyleneimines). *Pharmacol. Exp. Ther.*, 100, 398-407, (1950).

RTECS (1998).

Rainbauer H. (1989). Untersuchung der Explosionsfähigkeit von 2 Staubproben. (Investigation on the explosibility of 2 dust samples). Testing laboratory: Sicherheitstechnische Prüfstelle. Report no.: 5028/89. Owner company: Chemserve Industrie Service GesmbH. Report date: 1989-11-23.

Ramusino MC, Vailati G (1982). Modifications in *Salmo Gairdneri* due to 2,4,6 Triamino 1,3,5 Triazine (Melamine). *Acta Embryol. Morphol. Expert* 3 (1), pp. 41-48. Testing laboratory: University of Milan, Department of Zoology.

Rao GN, Giesler PJ, Palmer TE, Mast RW, Friedman MA, Shaffer CB (1982). Chronic Toxicity of Melamine in Fischer 344 Rats. *Toxicologist* 2, p.179, Abstract No. 626. Testing laboratory: Raltech.

Reno FE (1983). 2-Years chronic feeding study of melamine in Fischer 344 rats. Testing laboratory: Hazelton Raltech Inc. Owner company: American Cyanamid Co. Study number: 79016. Report date: 1983-07-06.

Reuse P and Holzschuh O (2009). Determination of some physical-chemical properties of Melamine. Testing laboratory: Institute of Safety and Security. Swissi. Report no.: 204611.08.0640.02. Owner company: AMI Agrolinz Melamine International GmbH. Report date: 2009-02-12.

Rijcken WRP (1995). Primary skin irritation / corrosion study with melamine in the rabbit. Testing

laboratory: NOTOX B. V., 5231 DD 's-Hertogenbosch. Report no.: 146205. Owner company: DSM N. V. Report date: 1995-07-06.

Roehrborn, G. (1959). Dros. Info. Serv., 33, 156, (1959); cited in ECB IUCLID4 2009.

Roehrborn, G. (1962). Z. Vererbungslehre, 93, 1-6 (1962); cited in ECB IUCLID4 2009.

Rossman TG, Molina M, Meyer L, Boone P, Klein CB, Wnag Z, Li F, lin WC, Kinney PL (1991). Performance of 133 compounds in the lambda prophage induction endpoint of the Microscreen assay and a comparison with *S. typhimurium* mutagenicity and rodent carcinogenicity assays. *Mutat. Res.*, 260, 349-367, (1991).

Sadtler Sadtler standard spectra. Sadtler standard spectra, Philadelphia, Pa., Sadtler Research Lab.; cited in ECB IUCLID 2009.

Sakazaki H, Ueno H, Umetani K, Utsumi H, Nakamuro K (2001). Immunotoxicological Evaluation of Environmental Chemicals Utilizing Mouse Lymphocyte Mitogenesis Test. *J. Health Sci.*, Vol. 47(3), 258-271, 2001.

Sasaki S (1978). The Scientific Aspects of the Chemical Substance Control Law in Japan. *Aquatic Pollutants: Transformation and Biological Effects*, 283-298.

Seiler JP (1973). A survey of the mutagenicity of various pesticides. *Experientia*, 29, 622-623, (1973).

Selden JR, Dolbeare F, Clair JH, Miller JE, McGettigan K, DiJohn JA, Dysart GR, DeLuca JG (1994). Validation of a flow cytometric in vitro DNA repair (UDS) assay in rat hepatocytes. *Mut. Res. DNA repair* 315, 147-167, (1994); cited in ECB IUCLID4 2009.

Shaffer CB (1955). Melamine: Acute and Chronic Toxicity. unpublished report. Testing laboratory: Hazleton Laboratories, Virginia. Report no.: 55-21. Owner company: American Cyanamid Company. Report date: 1955-06-15.

Shelby M. D., Erexson GL, Hook GJ, Tice RR (1993). Evaluation of a Three-Exposure Mouse Bone Marrow Micronucleus Protocol: Results with 49 chemicals. *Environmental and Molecular Mutagenesis*, 21, pp. 160-179.

Sorg RM (1981). Genetic Toxicology - Micronucleus Test (MNT). Testing laboratory: Pharmakon Research International, Inc. Owner company: American Cyanamid Co. Study number: PH 309A-AC-001-81. Report date: 1981-10-19.

Sorg RM (1982). In vitro sister chromatid exchange in Chinese hamster ovary cells. Testing laboratory: Pharmakon Research International, Inc. Owner company: American Cyanamid Co. Study number: PH 319-AC-002-82. Report date: 1982-05-20.

Sugita T, Ishiwata H, Maekawa A (1991). Intestinal Absorption and Urinary Excretion of Melamine in Male Wistar Rats. *J. Food Hyg. Soc. Japan*, Vol. 32, No. 5, pp. 439-443.

Swope G, Kenna M (1950). Effect of organic compounds on biochemical oxygen demand. *Sewage and industrial waste engineering* 21, 467-468.

Taeger (1992). Prüfung der biologischen Abbaubarkeit bzw. der Eliminierbarkeit von Melamin im Standardversuch nach Zahn Wellens (biodegradation of Melamine Zahn-Wellens test). Testing laboratory: BASF Aktiengesellschaft, Labor für Mikrobiologie. Owner company: BASF AG. Study number: 92/2364/10/1. Report date: 1993-06-14.

Taeger (1993). Prüfung der biologischen Abbaubarkeit bzw. der Eliminierbarkeit von Melamin im Standardversuch nach Zahn-Wellens (Biodegradation of Melamine: Zahn-Wellens test). Testing laboratory: BASF Aktiengesellschaft, Labor für Mikrobiologie. Owner company: BASF AG. Study number: 93/2364/10/2. Report date: 1993-06-14.

Thiersch J. B. (1957). Effect of 2,4,6, Triamino-"S"-Triazine (TR), 2,4,6, "Tris" (Ethyleneimino) -"S"-

Triazine (TEM) and N, N', N"-Triethylenephosphoramidate (TEPA) on Rat Litter in Utero. Proc. Soc. Biol. Med., 94, 36-43, (1957).

Tillmann (1990). Sauerstoffverbrauchstest (oxygen consumption test). Testing laboratory: Labor für Ökologie, BASF Aktiengesellschaft. Report no.: 10/0295/88. Study number: 01/88/0295. Report date: 1990-11-23.

Tyl RW, Mast RW (1982). Evaluation of Urolithiasis Induction by Melamine (CAS no. 108-78-1) in Male Weanling Fischer 344 Rats. Testing laboratory: Research Triangle Institute. Report no.: 31T-2407. Owner company: American Cyanamid Co. Study number: Rt82-MEL. Report date: 1982-11-30.

Ubaydullayev RU, Kamil'dzhanov AKh, Mirzayev ShM, Ashryatova NKh (1993). Establishment of the maximum permissible concentration of melamine in atmospheric air. Gigiena i Sanitariya, 58 (1993), pp. 14-16. Original in Russian. An English translation was obtained. Testing laboratory: Scientific Research Institute for Sanitation, Hygiene and Occupational Health, Uzbek Ministry of Health, Tashkent.

Ullmann; Chapter prepared by Crews GM, Ripperger W, Kersebohm DB, Günther Th, Mertschenk B (2006). Melamine and Guanamines. Ullmann's encyclopedia of industrial chemistry. Chapter on melamine and guanamines. Wiley-VCH Verlag, Weinheim.

Unknown. (1990). Acute Toxicity Data. J. American College Toxicol 1, 110 (1990); cited in RTECS and in ECB IUCLID4 2009.

Vaessen P (1982). Onderzoek naar de acute toxiciteit van DSM melamine in water voor *Poecilia reticulata* (Investigation of the acute toxicity of melamine in water to *Poecilia reticulata* (Guppy)). Testing laboratory: DSM. Report no.: CRO MK 82 236 MR-1. Owner company: DSM. Report date: 1982-02-26.

Worzalla JF, Kaiman BD, Johnson BM, Ramirez G, Bryan GT (1974). Metabolism of Hexamethylmelamine-Ring-14C in Rats and Man. Cancer Research 34, pp. 2669-2674.

Yang F, Yu Mao Y, Zhang X, Ma Z, Zhang X (2009). LC-MS/MS method for the determination of melamine in rat plasma: Toxicokinetic study in Sprague-Dawley rats. J. Sep. Sci. 2009, 32, 2974-2978.