

**SAFETY/RISK
ASSESSMENT FOR
MELAMINE AND
ANALOGUES**

FDA SCIENCE BOARD

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MELAMINE COMPOUNDS S/RA

■ Purpose

- Evaluate the risk to humans from consumption of pork, chicken, eggs, and fish that had been inadvertently fed animal feed containing melamine and its analogues (MCs)



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- Safety/Risk Assessment Model
- Evaluation of Toxicity Information: NOAEL
- Application of Uncertainty/Safety Factors
- Development of Intake (Exposure) Scenarios
- Determination of Margins of Safety
- Calculation of Levels of Concern
- Peer Review Report Discussion
- Future Research Recommendations

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- Assumption: MC contamination is short term, not long term occurrence
- Toxicity data:
- Acute LD₅₀ in rats: 3161 mg/kg bw/day
- 13-week feeding study in rats: 63 mg/kg bw/day (NOAEL) – used for S/RA
- 2-year bioassay in rats: 263 mg/kg bw/day
- 13-week feeding study in mice: 1600 mg/kg bw/day (NOAEL)

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- Observed toxicities with ingestion:
- Reduced food consumption
- Body weight loss
- Crystalluria and bladder stones
- Hyperplasia of urinary bladder epithelium
- No renal failure or symptoms of failure
- Dose to elicit toxicity varies widely with species, but symptoms are similar

MELAMINE COMPOUNDS S/RA

- Histopathology of cats who died from eating contaminated pet food showed abundant renal crystals.
- Subsequent analysis of crystals confirmed presence of melamine and cyanuric acid.

MELAMINE COMPOUNDS S/RA

- In NTP lifetime study, 263 mg/kg bw/day for two years in rats
- In male rats, increase in stones and tumors of the bladder
- Stones appear to be prerequisite for tumor formation
- Assume that MC are equipotent
- Toxicokinetics: well absorbed, distributed to body water, rapidly excreted in urine (1/2 life of 2-3 hours)
- No other tissues showed excess tumor formation

MELAMINE COMPOUNDS S/RA

- Assumptions for intake scenarios - MCs
- Treated all MCs as a group, not as single compounds
- Tissues were contaminated with 100 ppb = melamine @ 50 ppb; cyanuric acid, ammeline, ammeline combined @ 50 ppb
- FDA/FSIS data on tissue levels from hogs fed contaminated ration

MELAMINE COMPOUNDS S/RA

- 100 ppb: conservative estimate of the Limit of Detection to ensure conservative estimate of exposures
- All pork/poultry/fish/eggs were from animals fed contaminated feed until just prior to slaughter

Intake Scenario I, II, III

- Intake calculated from CSFII: 1994, 96, 98
- Sophisticated methodology using commodity codes and product recipes
- (I) Direct intake of catfish, chicken, pork, eggs
- (II) Intake: chicken & pork meat & byproducts
- (III) Worst case scenario: MCs in all solid foods at 100 ppb; results in 150 $\mu\text{g}/\text{p}/\text{day}$ -60 kg person

MARGINS OF SAFETY

- TDI: estimate of amount taken in per day over a lifetime without appreciable risk
- Point of departure (POD)=point of no animal toxicity=NOAEL of 63 mg/kg bw/day
- Then divide by 100-fold SF/UF (10-fold=interspecies; 10-fold=intraspecies variations)
- Resulting Tolerable Daily Intake (TDI)=0.63mg/kg bw/day (NOTE much <the NOAEL)

MARGINS OF SAFETY

- Margin of Safety (MOS) = divide TDI by the exposure estimate for various products:
- Catfish: 1853; Chicken: 3000; Eggs: 3938; Pork: 3706; Combined Products: 2625
- MOS for the worst case scenario (III) where all solid food is assumed to be contaminated with 100 ppb MC = 252-fold less than the TDI
- In other words, to get the TDI dose from food contaminated at the 100 ppb level, you would need to consume $1.5 \text{ kg} \times 252 = 378 \text{ kg} \times 2.2 \text{ lbs/kg} = 831 \text{ lbs}$ of food (over simplification)

MARGINS OF SAFETY

- LOC or Level of Concern = TDI (0.63 mg/kg/day) X 60 kg person / 90th %tile level of consumption (conservative assumption)
- Tells us that at the 90th %tile level of food consumption what level of MC contamination we can eat with no appreciable risk
- LOC for pork, poultry, eggs, catfish products: 194-450 ug/g (or mg/kg)

CONCLUSION

- Based on currently available data and information, the results of the safety/risk assessment indicate that the consumption of pork, chicken, domestic fish, and eggs from animals inadvertently fed animal feed contaminated with melamine and its analogues is very unlikely to pose a human health risk.

PEER REVIEW

- Interim S/RA for MC and charge were submitted to 6 outside expert reviewers
- Overall, there was consensus from the peer reviewers that the conclusions of the S/RA were appropriate. In addition, recognizing the time-sensitive context and need for the S/RA results, the peer reviewers concurred that the methodology, data, assumptions, and exposure scenarios used were appropriate.

POINTS TO CONSIDER

- Consider data from studies of similar compounds, e.g., "triazine" pesticides
- Evaluate possible chronic toxicity from longer duration exposure
- Provide more information on the design of specimen sampling and toxicology studies

RESEARCH RECOMMENDATIONS

- Determine the concentration and crystallization of MCs in urine of different species
- Consider possible formulation of other (more toxic) compounds during heating
- Study whether co-exposures to multiple MCs elicit additive or synergistic effects.
- Improve analytical methods, especially in detection of low levels of MCs in tissues of food-producing animals
- Characterize renal crystals

RESEARCH RECOMMENDATIONS

- Conduct basic toxicological studies in multiple species
- Develop early biomarkers for onset of renal failure
- Study effects of dehydration, common medications (diuretics), and other effects/agents on renal excretion of MC
- Conduct longer term toxicology studies to assess potential carcinogenic, reproductive and developmental effects