Consumers Union
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Secretary-Designate Tom Daschle
US Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

The Honorable Andrew C. von Eschenbach, M.D., Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane, Room 15-47
Rockville, MD 20857

Dear Secretary-Designate Daschle and Commissioner Von Eschenbach:

Consumers Union is concerned about safety risks in infant formula produced in the United States and urges FDA to move quickly during the administrations' transition period to expand testing of formula and recall all products that test positive for melamine or its analogues including cyanuric acid. Six infants have died in China due to consumption of contaminated formula and almost 300,000 have been made ill. On December 22, 2008, FDA posted new test data that showed that a total of 4 samples of US-made infant formula out of 89 tested were positive for melamine or an analogue, cyanuric acid, a rate of almost 5 percent contamination. Three of these samples came from one type of formula, Mead Johnson's Enfamil with Iron, the fourth from Nestle's Good Start Supreme with Iron.

FDA originally stated in a risk assessment published on October 3, 2008 that there was no level of melamine and its analogues that FDA regarded as safe in infant formula: "FDA cannot establish a level of melamine and its analogues in these [infant formula] products that does not raise public health concerns."[1] On November 28, 2008, after FDA detected melamine in infant formula, it revised that opinion, stating that 1 ppm of melamine or one of it analogues alone in infant formula was safe[2]. All four of these positive samples were under the 1 ppm limit (from 0.137 to 0.412 ppm). We believe, however, that FDA's initial judgment was correct and that no amount of these chemicals should be allowed in infant formula.

FDA's November risk assessment is seriously flawed, because, unlike the October risk assessment, it only considers the toxicity of melamine alone, and chooses to ignore scientific data on the effects of melamine in combination with its analogue cyanuric acid, which FDA has also found in infant formula. In fact, the two together appear to be far more toxic than

Consumers Union
Headquarters
101 Truman Avenue
Yonkers, New York 10703-1057
914-378-2000
fax: 914-378-2900

[1] http://www.cfsan.fda.gov/~dms/melamra3.html
[2] http://www.cfsan.fda.gov/~dms/melamra4.html

melamine alone. One study found that half the amount of melamine that FDA uses as its benchmark "no effect" level for melamine alone, when fed to cats in combination with an equal amount of cyanuric acid, was so acutely toxic to the cats' kidneys, that they had to be euthanized within 48 hours.[3]

Consumers Union believes that FDA should regulate infant formula based on an assumption that infants may be exposed to melamine and cyanuric acid in combination--as would happen if an infant consumed a bottle of a formula contaminated with melamine followed by one contaminated with cyanuric acid. Under this realistic scenario or the possibility that these related compounds can occur in concert, FDA must conclude, as it did in October, that it does not presently have the scientific data to justify allowing any of either of these contaminants in infant formula.

FDA should conduct a much larger testing program of US-made infant formula, to determine the extent to which melamine and cyanuric acid appear in them, in what brands they appear, and whether in any samples they occur together. We also urge FDA to conduct animal studies to determine the toxicity of melamine and cyanuric acid in combination, using the most sensitive test species. Until such time as it has better scientific data in hand, FDA should not allow any level of melamine or its analogues in infant formula, and should recall any products in which these chemicals are detected.

FDA Should Expand Its Testing of Infant Formula for Melamine and Its Analogues

While we recognize that the transition to a new Administration is imminent, we would hope that FDA could immediately undertake a substantial infant formula testing program for melamine and its analogues including cyanuric acid. FDA test data on 89 samples of US-made infant formula, posted on the FDA website in November and December, 2008, show that one sample was contaminated with melamine, and three more with a closely related chemical, cyanuric acid. Four positive results out of 89 is a high rate, some 4.5 percent. In addition, some companies appeared to have particularly high rates. For example, only five Nestle samples were tested, and one was positive, a rate of 20% contamination; for Mead Johnson, the rate was 14% (3 of 21 samples were positive). These data signal that much more testing should be done.

In addition, FDA has not equally sampled products of all producers. For Abbott, Mead Johnson, and PBM, FDA tested 38, 21 and 25 samples, respectively. However, for Nestle, FDA tested only 5 samples. Since one of these five came up positive for melamine, it is imperative that FDA test many more samples to determine the extent of the contamination in Nestle products.

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[3] Puschner, B, Poppenga, RH, Lowenstine, LJ, Filigenzi, MS and PA Pesavento. 2007. Assessment of melamine and cyanuric acid toxicity in cats. *Journal of Veterinary Diagnostic Investigation* 19: 616-624.

FDA testing so far is much too limited to assess the scope of the contamination problem in the United States. FDA must test hundreds more samples before it can have an accurate idea of how many samples may be contaminated, the levels of contamination, any brand differences, and what forms of melamine and its analogues, including cyanuric acid, are involved.

FDA Should Have a Zero Tolerance in Infant Formula for Melamine and its Derivatives

Consumers Union believes that FDA was correct in October when it stated that "FDA cannot establish a level of melamine and its analogues in these (infant formula) products that does not raise public health concerns."[4] FDA explained its conclusion as follows: "several significant gaps in our scientific knowledge about melamine and its analogues toxicity regarding infants exist, including:

1. The impact of the presence of more than one melamine analogue which has the potential to increase the toxicity of the adulterated infant formula.
2. The consequences of continuous use of these infant formulas as sole source of nutrition.
3. The possibility that these formulations can be fed as the sole source of nutrition to premature infants with immature kidney function and even greater intake of infant formula per unit body weight for a longer time period than term infants."

In other words, in October, FDA felt that there was no level of melamine or its analogues that could be regarded as safe in infant formula, because not enough is known about the toxicity of melamine and cyanuric acid together, not enough is known about the consequences of continuous consumption of formula by infants, and not enough is known about potential effects on premature infants.

Consumers Union is particularly worried that melamine and cyanuric acid may occur in combination in infant formula, something broader testing would shed light upon. However, there is also ample reason to worry that if melamine is present in one brand of formula, and cyanuric acid is present in another, as current tests have already shown, then infants may be exposed to both together. The chemicals may be combined in an infant's digestive system or kidneys if the infant is fed two different formulas. For example, one parent who recently contacted Consumers Union indicated that she routinely fed her baby Enfamil and Similac, alternating the two. Sometimes both formulas were fed in the same feeding. She did this because one caused constipation, and one caused loose bowels, but together the baby's digestion seemed just right.

Unfortunately, since November FDA has regulated melamine based only on the toxicity of melamine alone. This is not an appropriate benchmark for safety. As FDA is aware the combination of melamine and cyanuric acid is more toxic than either one alone.

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[4] http://www.cfsan.fda.gov/~dms/melamra3.html

Individually, both melamine and cyanuric acid have low acute toxicities (LD_{50s} over 3,000 mg/kg body weight). Both are water soluble and so move through the body fairly quickly, both having half-lives of roughly three hours[5]. However, when melamine and cyanuric acid, which are structurally related, occur together, particularly under acidic conditions, they precipitate out of solution, forming insoluble crystals (called melamine cyanurate). These crystals accumulate in the kidney and its tubules, thereby leading to obstructive renal failure. These facts came to light as a result of the investigation of the melamine pet food contamination scandal of 2007, which is believed to have affected thousands of dogs and cats. A key paper, authored by scientists from Proctor & Gamble and FDA demonstrated melamine cyanurate crystals as the toxic contaminant of pet food and notes that these crystals could be found in the kidneys of affects cats and dogs, in the pet food, and in the suspect "wheat gluten," a pet food ingredient imported from China.[6]

Two separate feeding studies in different animal species have established that melamine and cyanuric acid consumed together can result in the formation of melamine cyanurate in the kidneys, seriously damaging them. In both studies the lowest doses tested caused adverse effects. A small feeding study involving cats found that the lowest dose of melamine and cyanuric acid tested—32 mg/kg body weight/day for each or total of 64 mg/kg bw/d—lead not just to a simple adverse effect but to kidney failure. The researchers called for more research to determine a "no-observable-adverse-effect level" (NOAEL): "This study has shown that a single oral exposure of cats to melamine and cyanuric acid at a concentration as low as 32 mg/kg each can result in acute renal failure . . . . *future research studies are needed to determine the lowest dose of melamine and cyanuric acid that can cause renal failure*"[7] *italics* added.

A second feeding study involving rats dosed with two separate mixtures—either 400 mg/kg/day each of melamine and cyanuric acid (e.g. ratio of 1:1), or 400 mg/kg/day melamine plus 40 mg/kg/day each of ammeline, ammelide and cyanuric acid (e.g. ratio of 10:1:1:1)—found that both mixtures produced renal toxicity."[8] Since melamine cyanurate is roughly a 1:1 mixture of melamine and cyanuric acid, the 10:1:1:1 mixture could be seen as producing melamine cyanurate in roughly a concentration of 80 mg/kg/day (e.g. 40 mg/kg/day melamine and 40 mg/kg/day cyanuric acid). Thus, in both the cat and the rat feeding studies, the lowest doses tested (64 mg/kg/day and 80 mg/kg/day, respectively) caused adverse effects. Thus, a lowest-observed-adverse-effect-level (LOAEL) has yet to be determined for melamine and cyanuric acid together. The NOAEL, of course, is even lower than the LOAEL.

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[5] Puschner, B, Poppenga, RH, Lowenstine, LJ, Filigenzi, MS and PA Pesavento. 2007. Assessment of melamine and cyanuric acid toxicity in cats. *Journal of Veterinary Diagnostic Investigation* 19: 616-624.

[6] Dobson, RLM, Motlagh, S, Quijano, M, Cambron, RT, Baker, TR, Pullen, AM, Regg, BT, Bigalow-Kern, AS, Bennard, T, Fix, A, Reimschuessel, R, Overmann, G, Shan, Y and GP Daston. 2008. Indentificaiton and characterization of toxicity of contaminants in pet food leading to an outbreak of renal toxicity in cats and dogs. *Toxicological Sciences* 106(1): 251-262.

[7] Puschner et al. 2007 OP CIT, pg. 622

[8] Dobson et al. 2008 OP CIT, pg. 255.

If we assume that the NOAEL for melamine and cyanuric acid together is only 10-fold smaller than the lowest level tested in the cat study (a very conservative assumption), this would give a NOAEL of 6.4 mg/kg body weight. Incorporating a safety factor of three orders of magnitude (10-fold for animal, not human, study, 10-fold for differences among human population, and 10-fold for infants) would give a safe combined level of melamine and cyanuric acid together of 0.100 ppm (or 0.050 ppm melamine and 0.050 ppm cyanuric acid) for infant formula. If we assume the NOAEL for melamine and cyanuric acid together is 100-fold smaller than the lowest level tested in the cat study (not an unreasonable assumption given that the lowest dose tested had such a catastrophic negative effect on renal function after a single meal that the cats had to be euthanized within 48 hours) this would result in a "safe" level of melamine and cyanuric acid of 0.010 ppm (or 0.005 ppm melamine and 0.005 ppm cyanuric acid). The four positive tests for infant formula were roughly 0.14 ppm for melamine and ranged from 0.245 ppm to 0.412 ppm for cyanuric acid. Although melamine and cyanuric acid were not found together in the infant formula, if they had been, or these two formulas had been consumed together, this dose would have been at least 1.4 to 14 times higher than an estimated "safe level" based on the cat study.

The facts that melamine and cyanuric acid were found in a relatively small (only 89) sampling of infant formula, at levels that, if found together, would likely exceed the estimated safe level; and that in a cat study the lowest dose of melamine and cyanuric acid tested together caused catastrophic adverse health effects, clearly shows the absolute urgency of determining a NOAEL for the combination. FDA should immediately conduct the necessary scientific research to determine the NOAEL for melamine and cyanuric acid together. We also urge FDA to use the most sensitive test species[9].

We also note that the incidence of kidney stones among children appears to be rising in recent years according to a number of doctors.[10] Whether low levels of melamine and cyanuric acid in formula and other foods have played any role in this increase is a question that needs to be answered.

Because FDA does not have the scientific knowledge at this point to set a safe level that takes into account the interaction of melamine and cyanuric acid in the body to form kidney stones, and that preterm infants may have immature kidney functions, FDA should not permit either of these chemical in infant formula. Any products in which they are found should be recalled.

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[9] The WHO/FAO Expert meeting to review toxicological aspects of melamine and cyanuric acid, held in Ottawa, Canada last month noted that such studies are underway in the US involving pigs, rats and cattle (at http://www.who.int/foodsafety/fs_management/conclusions_recommendations.pdf). We are not sure that pigs or cattle will be more sensitive to combination of melamine and cyanuric acid than cats, but urge FDA to use the most sensitive species.

[10]http://www.nytimes.com/2008/10/28/health/28kidn.html?_r=1&scp=1&sq=kidney%20stones%20in%20children&st=cse

FDA Should Recall Any Contaminated Infant Formula

While the FDA is conducting additional testing, FDA should:
(1) Recall all batches of formula containing detectable amounts of these chemicals in FDA testing
(2) Require formula manufacturers to test all batches of production and to not sell any formula that contains melamine or its derivatives.

We would hope that FDA take these steps as quickly as possible to protect the safety of infant formula.

Sincerely,

Jean Halloran
Director, Food Policy Initiatives

Michael Hansen Ph.D.
Senior Scientist

Urvashi Rangan Ph.D.
Senior Scientist

Cc:
David Acheson, M.D., Assistant Commissioner for Food Protection
Stephen Sundlof, D.V.M., Ph.D., Director, CFSAN
Frank Torti, M.D., M.P.H., Principal Deputy Commissioner and Chief Scientist
Michael Taylor, J.D, Research Professor, George Washington University