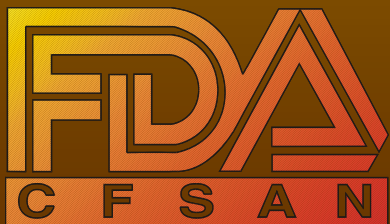


Enterobacter sakazakii

US and International Regulatory Efforts

Don L. Zink, Ph.D.
Center for Food safety and Applied Nutrition
U.S. Food and Drug Administration
College Park, Maryland



US Regulatory History

- Infant Formula Act of 1980 – 21 CFR Part 412
 - Gives FDA authority to establish quality-control procedures for infant formula manufacturing, as well as additional authorities
- 1986 Amendments to the Infant Formula Act
 - Requires that the Secretary issue regulations establishing requirements for quality factors and CGMPs, including quality control procedures, among other requirements
- In 1996, FDA published an ANPR to begin the regulatory process for implementing the 1986 requirements

Codex and International Regulations

- In 1979, Codex adopted the “Recommended International Code of Hygienic Practice for Foods for Infants and Children”
 - Described the general manufacturing controls and hygienic practices needed for the manufacture of infant formula and foods for young children
 - Recommended microbiological limits for infant formula and foods for children
- Many countries have microbiological and nutritional criteria for infant formula

Microbiological Standards

■ FDA (proposed in 1996 ANPR)

- Aerobic Plate Count - $\leq 10,000$ / gm
- Coliforms - ≤ 3.05 MPN / gm
- Fecal Coliforms - ≤ 3.05 MPN / gm
- *Salmonella* - n=60, c=0, m=0
negative
- *L. monocytogenes* - negative
- *S. aureus* - ≤ 3.05 MPN / gm
- *Bacillus cereus* - ≤ 100 / gm

Microbiological Standards

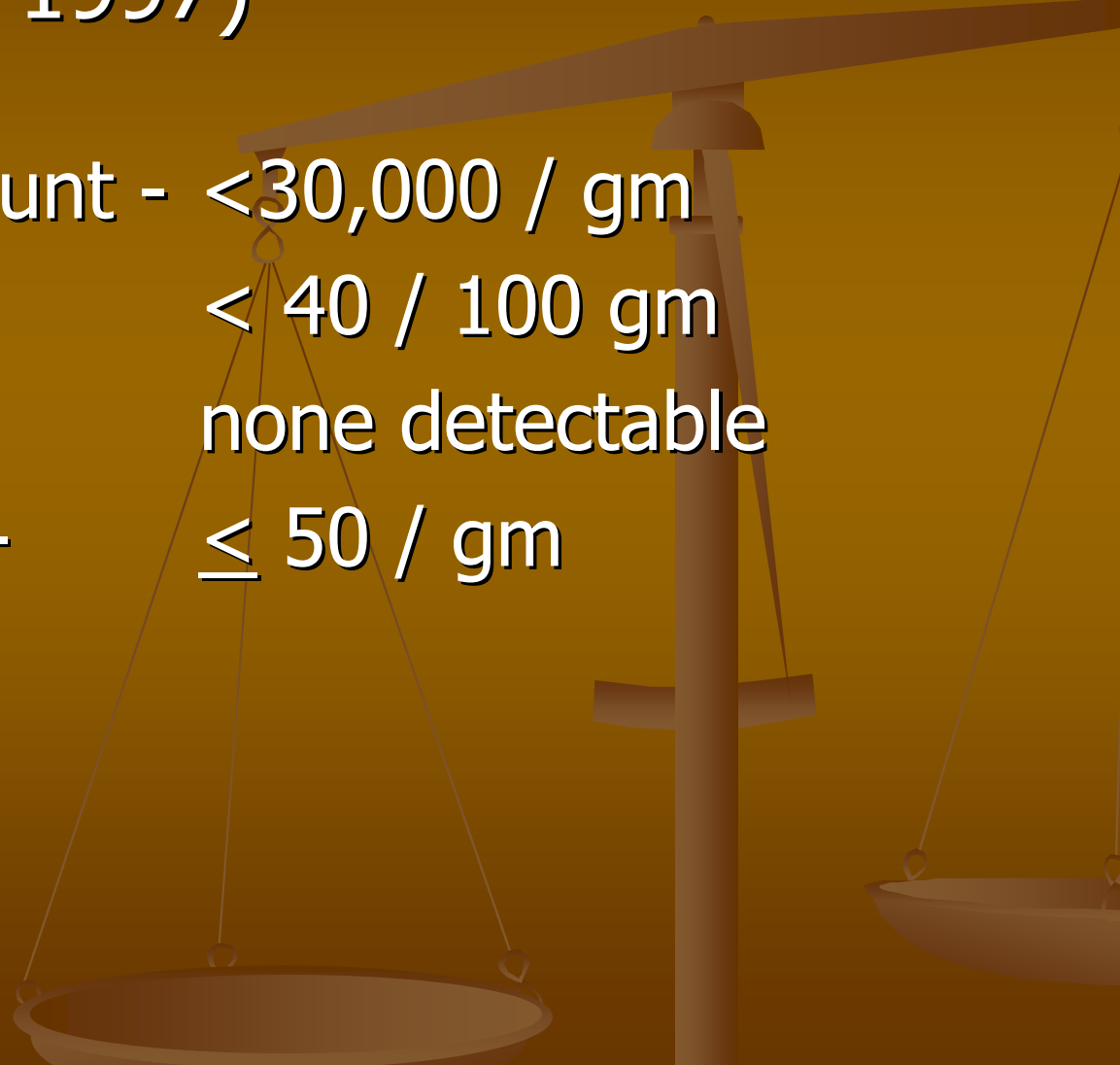
- CODEX Standards (limit per gram)
 - Aerobic Plate Count - $n=5, c=2, m=10^3, M=10^4$
 - Coliforms - $n=5, c=1, m < 3^*, M=20$
 - *Salmonella* - $n=60, c=0, m=0$

* <3 means no positive tube in a 3-tube MPN

From "Recommended International Code of Hygienic Practice for Foods for Infants and Children, CAC/RCP-21" (1979)

Microbiological Standards

■ China (GB10767-1997)

- Aerobic Plate Count - $< 30,000 / \text{gm}$
 - Coliforms - $< 40 / 100 \text{ gm}$
 - "Pathogens" - none detectable
 - Yeasts & Molds - $\leq 50 / \text{gm}$
- 

Microbiological Standards

- Canadian Standards (limit per gram)
 - Aerobic Plate Count - $n=5, c=2, m=10^3, M=10^4$
 - *Escherichia coli* - $n=10, c=1, m<1.8, M=10^1$
 - *Salmonella* - $n=20, c=0, m=0$
 - *Staph. aureus* - $n=10, c=1, m=10^1, M=10^2$
 - *Bacillus cereus* - $n=10, c=1, m=10^2, M=10^4$
 - *Cl. perfringens* - $n=10, c=1, m=10^2, M=10^3$

From "Health Products and Food Branch Standards and Guidelines for Microbiological Safety of Food, Interpretive Summary", Jan. 2003

The Dawn of *E. sakazakii*

- 1961 – Urmeenyi and Franklin, two fatal cases of neonatal meningitis in 1958 in England
- 1965 – Jøker *et al.*, neonatal meningitis in Denmark
- 1980 – Farmer *et al.*, identified dried milk as the source of one isolate
- 1983 – Muytjens *et al.*, 8 cases of neonatal Meningitis. Isolates from prepared formula.
- 1984 – Postupa and Aldova, isolated from powdered milk and powdered infant formula

The Dawn of *E. sakazakii*

Outbreaks of *E. sakazakii* infections linked to powdered infant formula: Historical cohort studies

- Simons et al. (1989): Enterobacter sakazakii Infections in Neonates Associated with Intrinsic Contamination of a Powdered Infant Formula (Infect Control Hosp Epidemiol)
- Van Acker et al. (2001): Outbreak of Necrotizing Enterocolitis Associated with Enterobacter sakazakii in Powdered Milk Formula (J Clin Microbiol)
- CDC. Enterobacter sakazakii Infections Associated with the Use of Powdered Infant Formula-Tennessee, 2001. MMWR 2002;51:297-300.

Recent Regulatory Activity

- 2003 – FDA issues a Federal Register Notice reopening comment on the 1996 ANPR
 - To update comments generally
 - To solicit comments on information presented at three public meetings in 2002 and 2003 – the risk of *E. sakazakii* was discussed at one of these meetings
- 2004 – FAO/WHO convened a meeting on *E. sakazakii* in powdered infant formula
 - *E. sakazakii* and *Salmonella* considered the pathogens of greatest concern

Recent Regulatory Activity

- March, 2004 – the 36th Session of the Codex Committee on Food Hygiene (CCFH) formed a working group to draft a revision of the code of practice for foods for infants
- November, 2004 – a working group drafted a revised code of practice focused on powdered infant formula
 - Proposed standard for *E. sakazakii* of negative in 30 x 10 gm samples
 - Proposed to replace coliform testing with *Enterobacteriaceae* – negative in 10 x 10 gm samples

Recent Regulatory Activity

- March, 2005 – 37th Session of CCFH reviewed draft code of practice for powdered infant formula
 - Broad agreement with the proposed *E. sakazakii* standard of neg. in 30 x 10gm sub-samples
 - Support for replacing coliforms with *Enterobacteriaceae*, but no consensus on proposed standard
 - Returned document to working group for further development

Regulatory Future



- Codex will adopt a revised code of practice that has *E. sakazakii* and *Enterobacteriaceae* standards
- The U.S. will pay close attention to the Codex process and publish a final rule on infant formula GMPs that incorporates microbiological criteria
- Improved test methodologies will be validated and adopted for enforcement use.
 - Ideally, we would like to have both a cultural and PCR method