

Micro-Nutrients in Milk and Dairy Products: New Insights and Health Benefits
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Dairy Products and Cancer: A Review of the Evidence

Johanna W. Lampe, PhD, RD

Division of Public Health Sciences

Fred Hutchinson Cancer Research Center, Seattle, WA



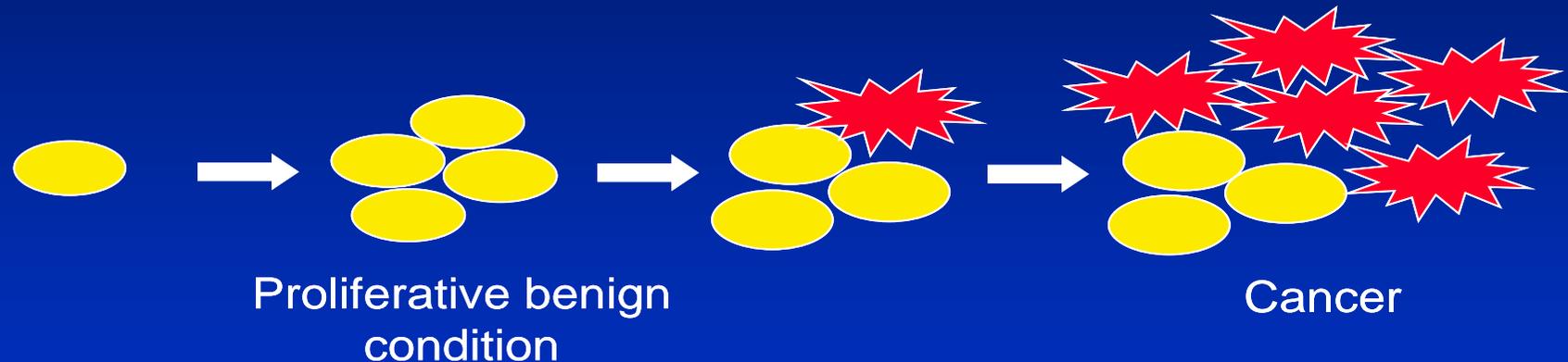
Outline



- How do cancers develop?
- What do we know about dairy products and cancer risk and prevention?
 - In humans
 - In animals
- By what mechanisms might compounds in dairy products influence cancer risk?

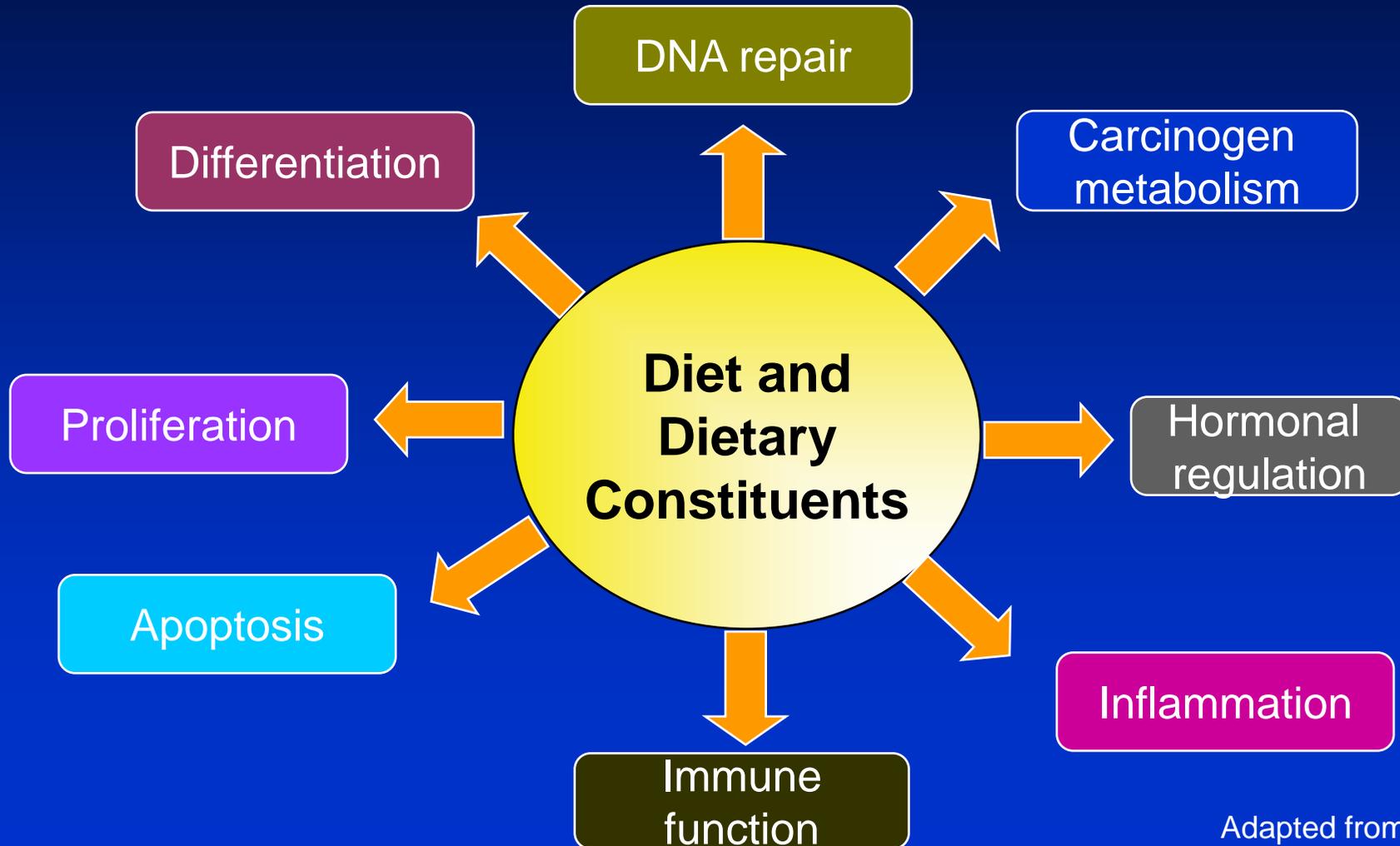
Cancer

- Class of 100+ diseases in which a group of cells display:
- **uncontrolled growth**
- **invasion** that intrudes upon and destroys adjacent tissues
- sometimes **metastasis**, or spreading to other locations in the body via lymph or blood



- Starts from a single cell that has lost control of its normal growth and replication processes due to changes in genetic information in the cell.
- Effect of genetic alterations or damage accumulated within cells over time.

Exposures and Cellular Processes Linked to Cancer



The Cancer Process Over Time

Pro-cancer Effects

Anti-cancer Effects

Failed
DNA Repair

Proliferation

DNA Repair

Apoptosis

Cell
differentiation

Normal cell

Damaged DNA

Somatic alterations of genes

Abnormal
DNA and cell division

Precancerous lesions/dysplasia

Cancer

Tumor Metastasis

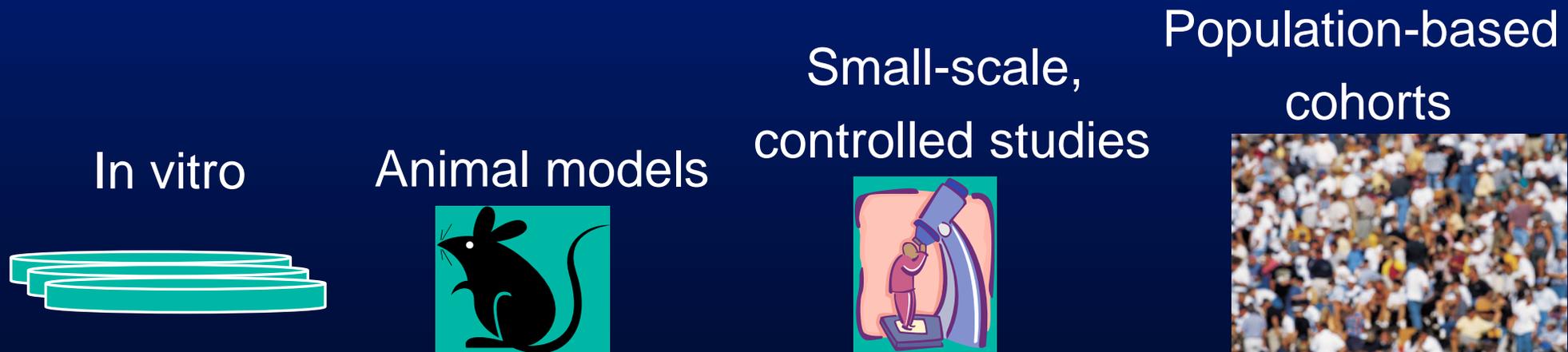
Cancer Considerations

- Cancers come in different flavors –
 - Carcinogens can have cell-specific effects
 - Cancers arise in different cell types in an organ
 - Cells can go bad in different ways – different tumor types
- Need to be careful generalizing across cancers
- Cancer preventive agents or foods can affect risk of different cancers differently:
 - what may be protective for one cancer may be a risk factor for another

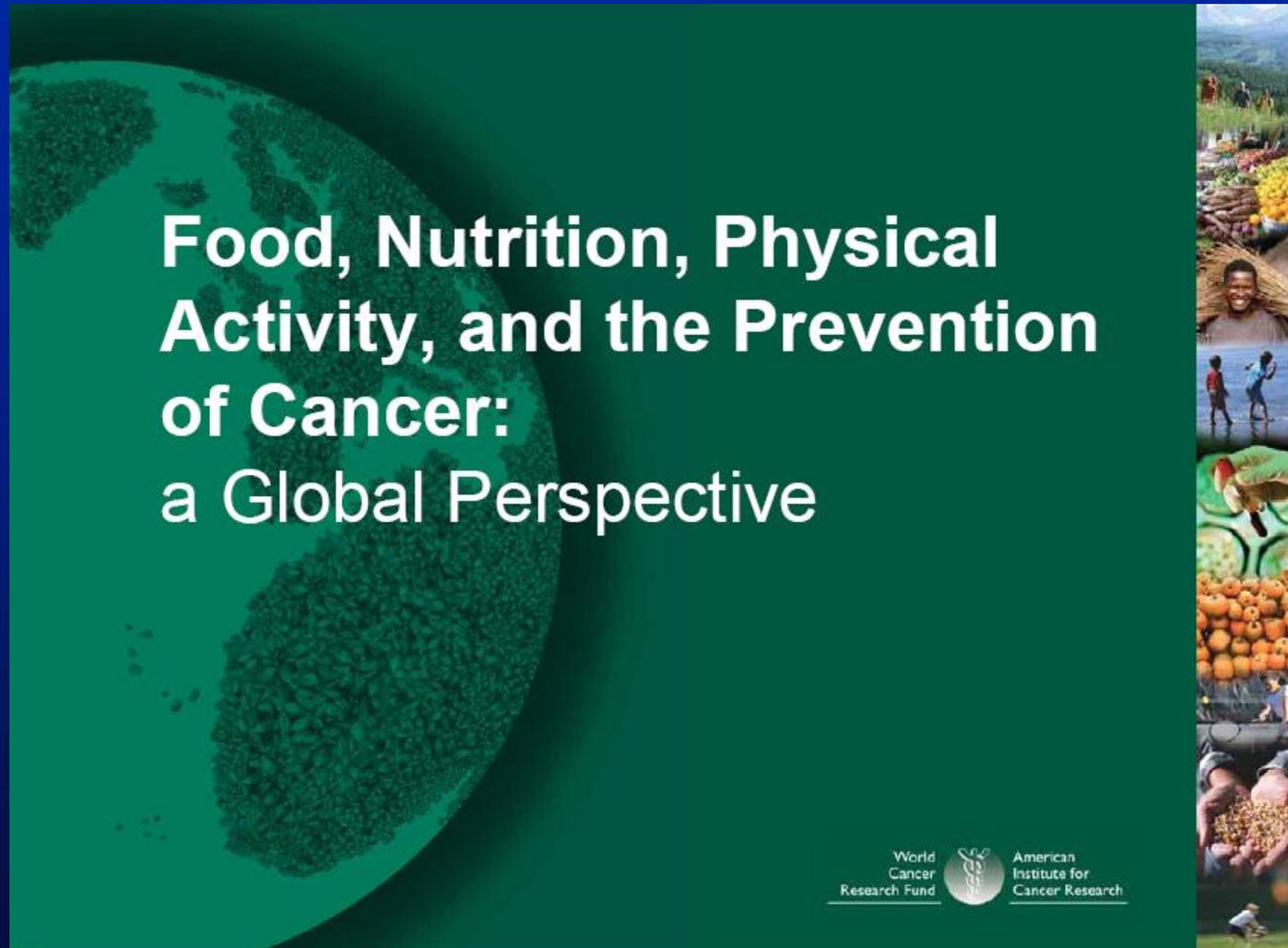
Dairy Products and Cancer

Sources and Weight of Evidence

- Across the continuum of research approaches
- Multiple human studies needed to provide sufficiently large sample sizes to evaluate effects at population-level.



Milk, Dairy Products, and Risk of Cancer



<http://www.dietandcancerreport.org> 2007

Milk, Dairy Products, and Risk of Cancer

Summary of WCRF/AICR Report

- Examined milk and dairy product intake in relation to 15 types of cancer
 - No association observed for:
mouth; pharynx and larynx; nasopharynx; lung; stomach; gall bladder; liver; breast; ovary; endometrium; cervix; kidney; and skin
 - Association reported for:
colorectal; bladder; prostate

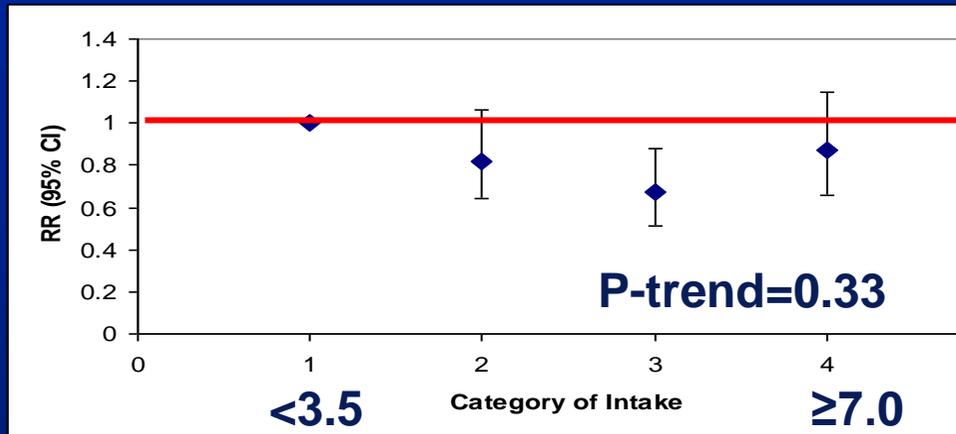


Milk, Dairy Products, and Risk of Cancer: Evidence from Human Population Studies

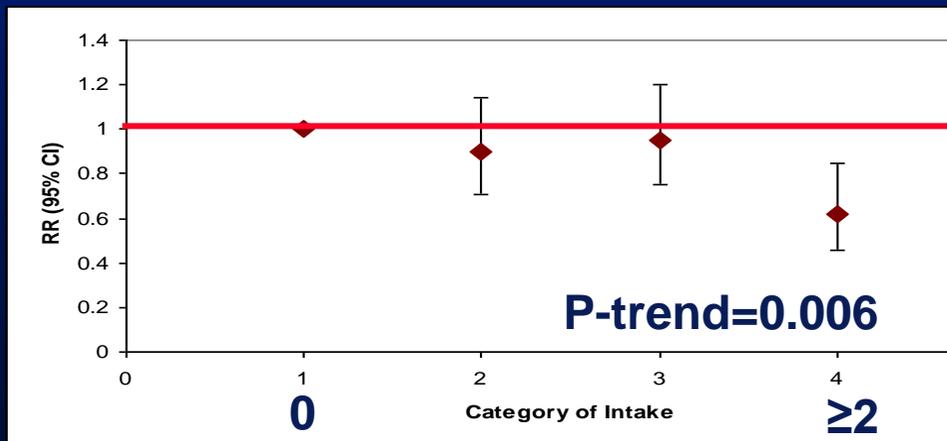
	DECREASED RISK		INCREASED RISK	
	Exposure	Cancer Site	Exposure	Cancer Site
Convincing	--	--	--	--
Probable	Milk	Colorectum	Diets high in calcium	Prostate
Limited -- suggestive	Milk	Bladder	Milk and dairy products	Prostate
			Cheese	Colorectum

Dairy Products and Bladder Cancer Risk in a Swedish Cohort

Total Dairy Products



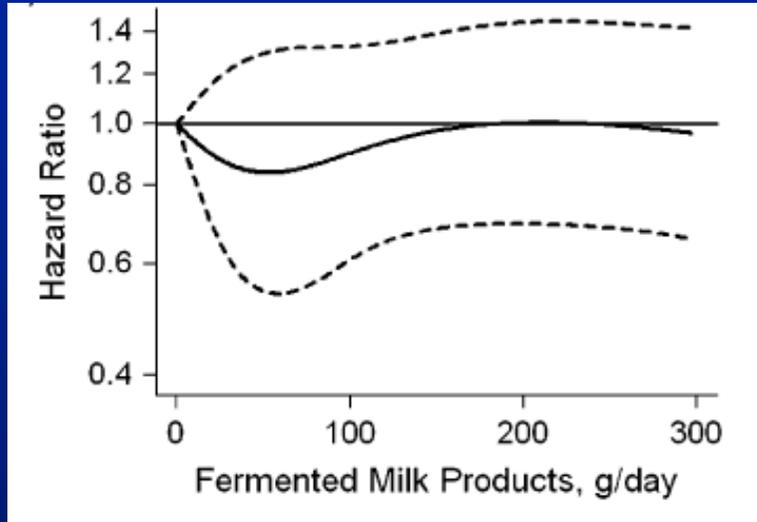
Cultured Milk Products



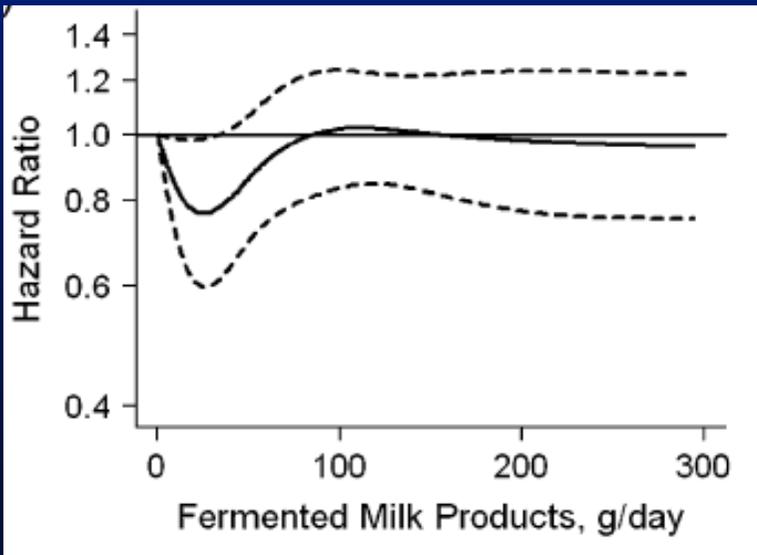
- Prospective cohort study of 82 022 Swedish men and women.
- Completed 96-item food frequency questionnaire in 1997
- 9.4 y of follow-up: 485 developed bladder cancer.
- No effect of total dairy, milk, and cheese, but 38% reduction in risk between no intake and highest quartile of cultured milk products.

Fermented Products and Bladder Cancer in Dutch Cohort

Men



Women



- Prospective cohort study of 120 852 men and women in the Netherlands Cohort Study on Diet and Cancer.
- Completed 150-item food frequency questionnaire in 1986
- 16.3 y of follow-up: 1549 developed bladder cancer.
- No effect of total dairy, but men and women in 2nd quintile of cultured milk products had 29% lower risk of bladder cancer.

Models adjusted for age, smoking status, number of cigarettes smoked, smoking duration, and intakes of vegetables, fruits, meat, beverages, energy, and fat.

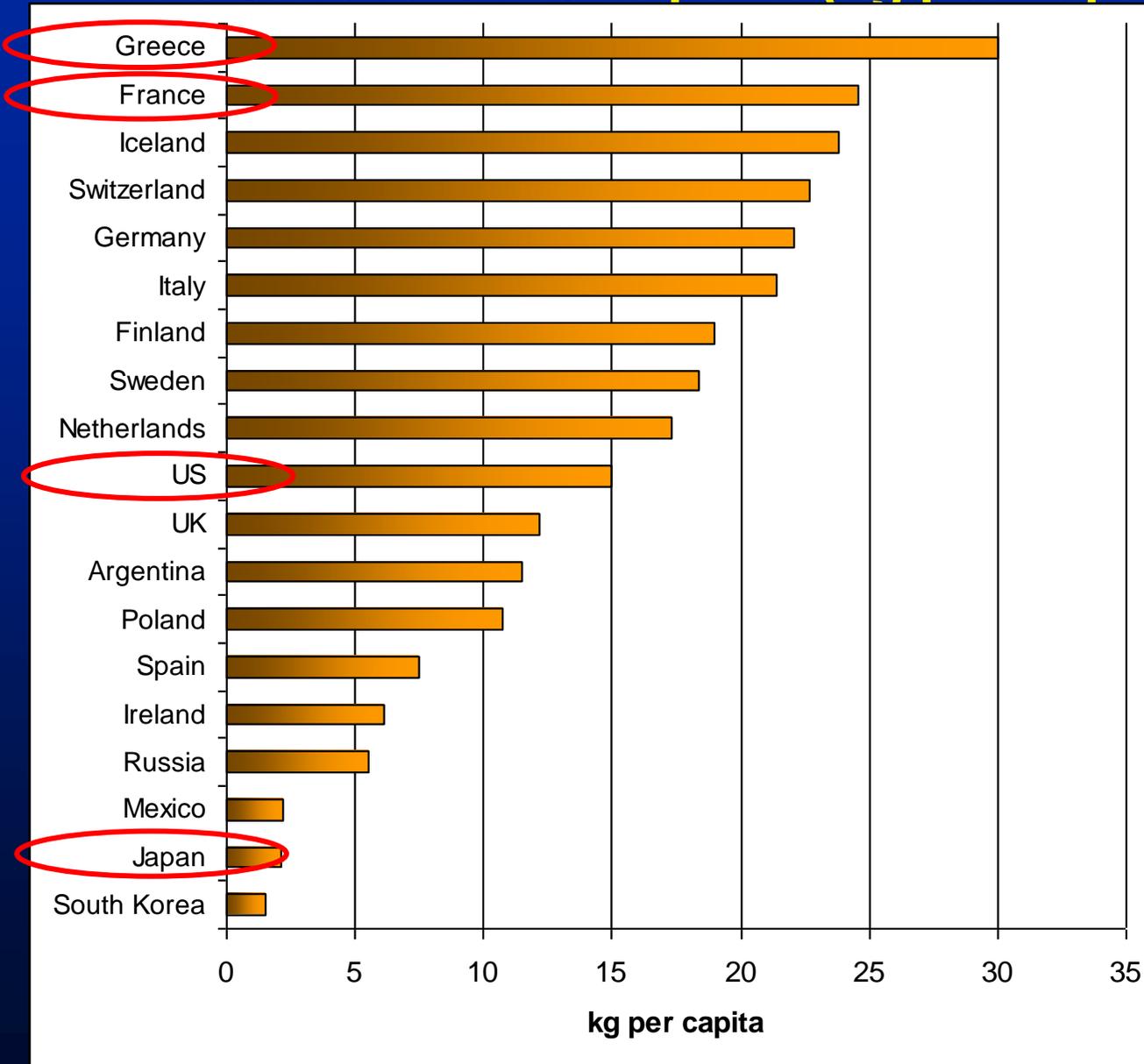
Studying Dairy Products and Cancer in the Context of the Human Diet



- To date, most studies are in high-income populations
- Amounts and types of dairy products consumed vary by population
- Traditionally, diets that include dairy products also include other healthy and less healthy foods.
- Need to consider dairy intake in the context of the overall diet.

Who Eats Cheese?

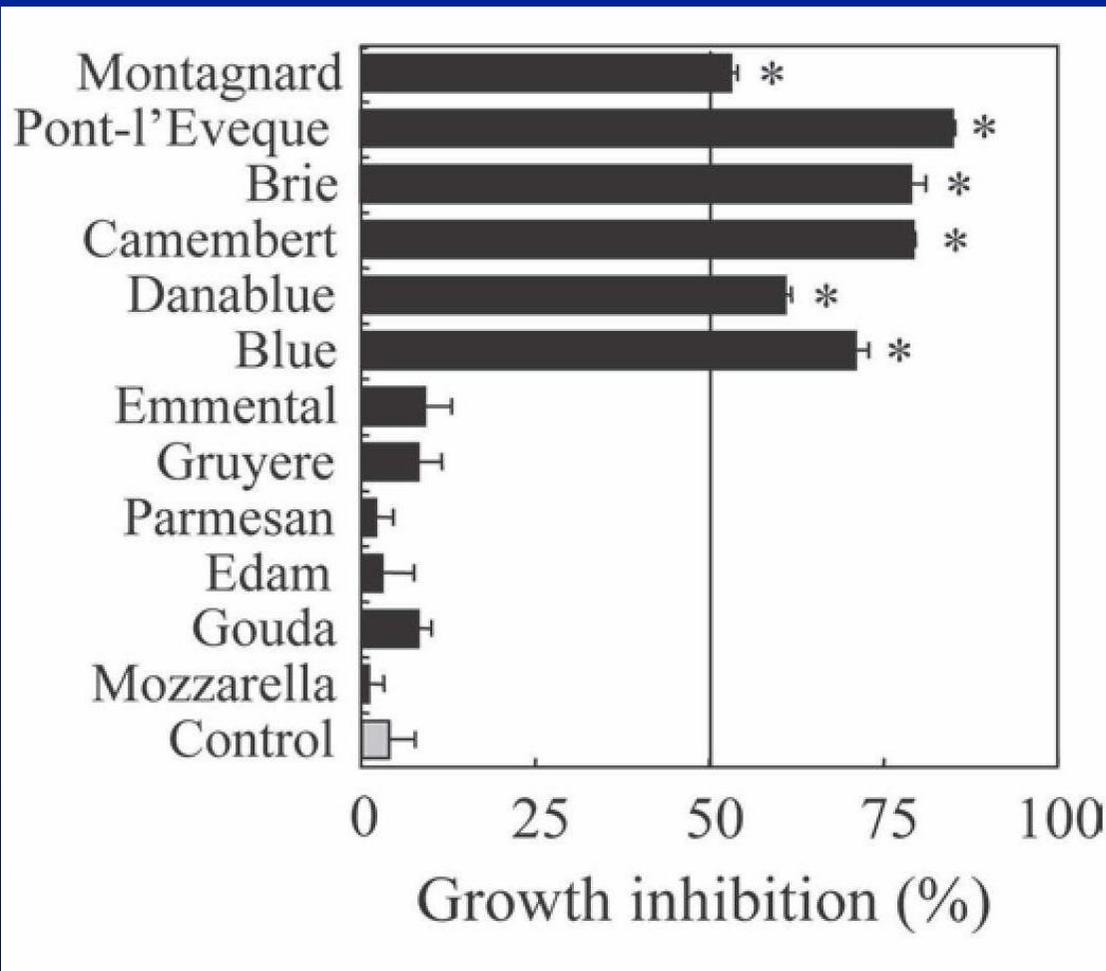
Total Cheese Consumption (kg per capita)



Feta
Emmental &
Camembert

Mozzarella

Cheese Type May Influence Cancer Risk: Effect of Cheese Extracts on Leukemia Cells



- Tested 12 cheese extracts on proliferation of human leukemia cells in culture
- Extracts of highly ripened cheeses inhibited growth of cells
- **Relevance of *in vitro* findings to humans?**
 - Bioavailability of active compounds?
 - Dose?

What micro-nutrients and other compounds in dairy products may influence cancer risk?

INCREASED RISK

- Calcium

DECREASED RISK

- Calcium
- Microbial fermentation products
 - Peptides
 - Fatty acids – conjugated linoleic acids
 - Vitamins -- vitamin K -- menaquinones
- Microbes



Calcium: Cell-Type Differences in Response

Increased Risk

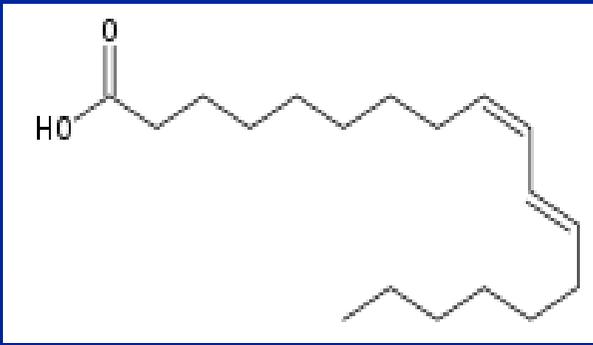
Prostate Cancer

- Increases insulin-like growth factor (IGF) 1 signaling, which increases cell proliferation.
- Suppress circulating 1,25OH vitamin D

Decreased Risk

Colorectal Cancer

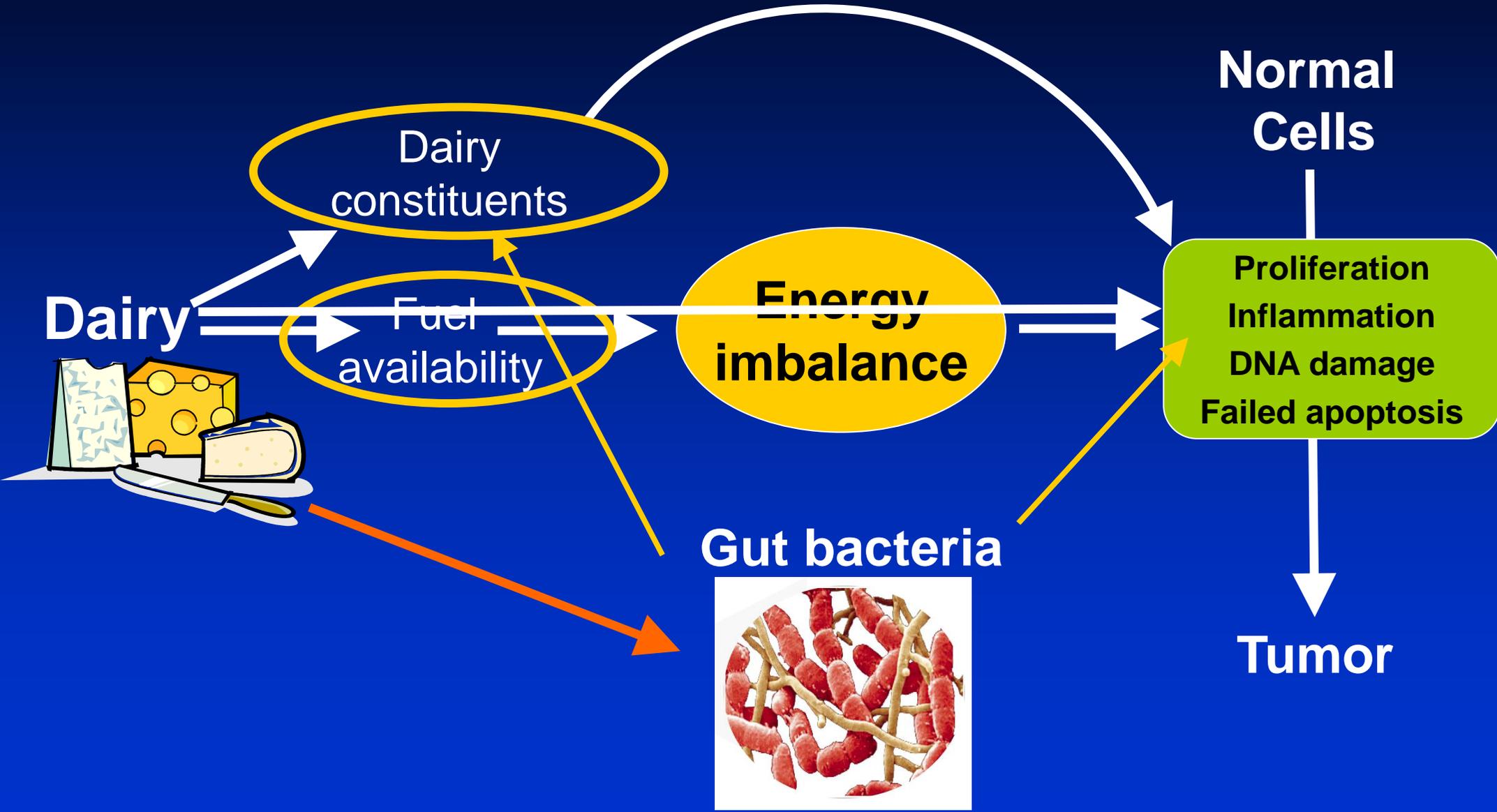
- High intracellular calcium favorably influences cell growth and apoptosis in colonic epithelium.
- Bind bile acids and fatty acids, preventing them from damaging colon cells.



Conjugated Linoleic Acid (CLA)

- Family of 28+ isomers of linoleic acid found especially in meat and dairy products derived from ruminants.
- Antioxidant and anti-inflammatory properties
- Anti-cancer effects in mice and rats
 - *Decreased growth of tumors in mammary, skin, and colon tissues.*
Kelley et al, *J Nutr* 137:2599, 2007
- 4 epidemiologic studies of breast cancer inconclusive
 - *3 case-control studies and 1 cohort study*

Relationship of Dairy Products, the Gut Microbiome, and Cancer Risk



Microbes and Cancer

- **Microbes as infectious agents**

- Account for ~20% of cancers worldwide
- Cervical, liver and gastric cancers
- Direct effects

- **Microbes as modifiers of physiology**

- **Microbes as modifiers of exposures**

- Metabolizing carcinogens, chemopreventive agents
- Affecting energetics

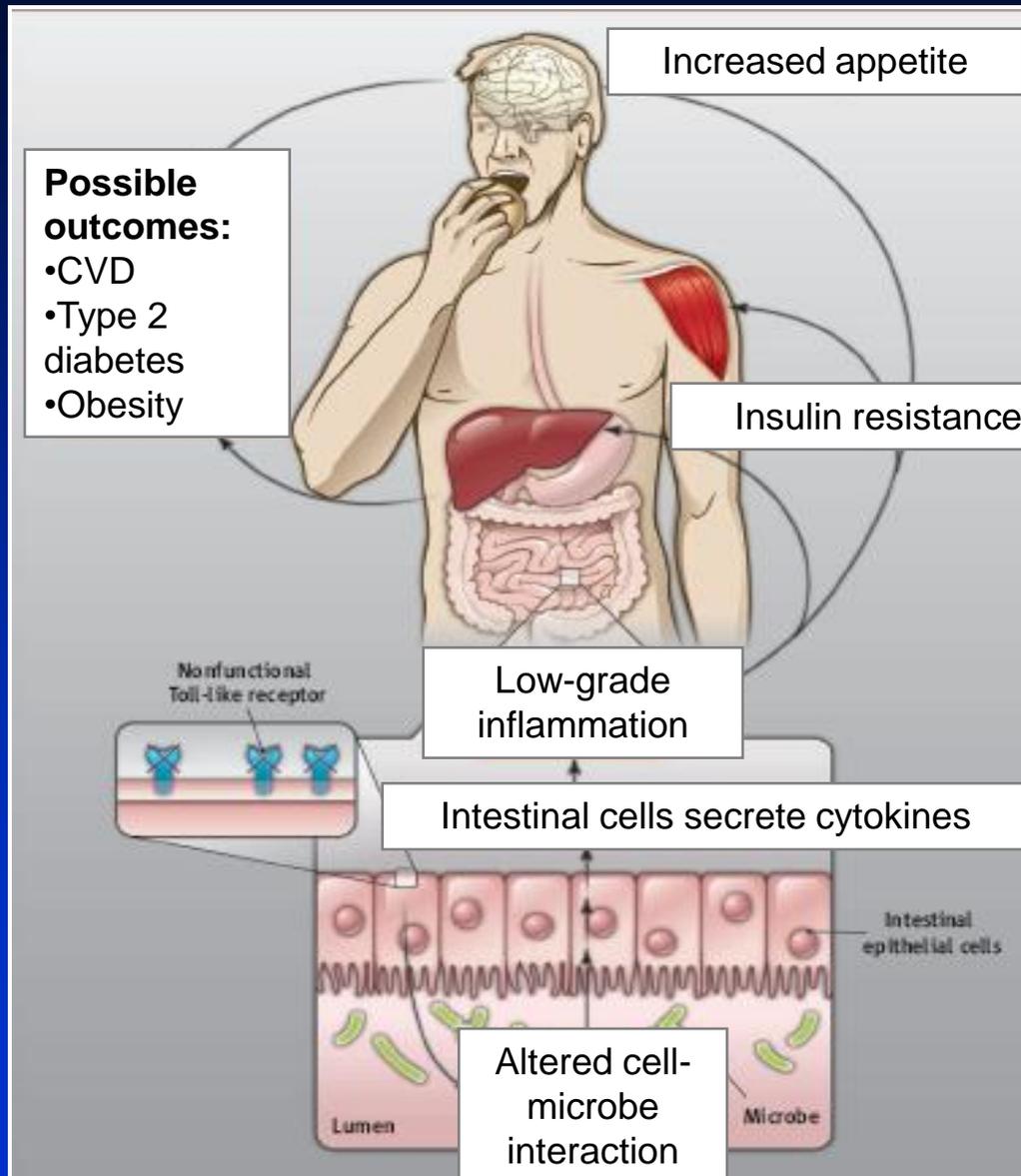
Mechanisms by Which the Gut Microbiome May Directly Influence Cancer Risk

- Reduce competition by less-desirable bacteria
- Interact with mucosal-associated immune system
- Regulate tight junctions and mucosal barrier function in epithelium
- Influence signal transduction pathways relevant to cell proliferation and apoptosis
- The gut microbiota:
 - The largest collection of microbes in the human body: ~10-100 trillion organisms
 - 100s of species in 6 main phyla

Cultured Dairy Products as Modifiers of the Gut Microbiome and Gut Physiology

- Source of probiotics, mostly lactic-acid bacteria and bifidobacteria.
- Modulation of inflammatory processes in the gut and ultimately systemically.

Gut Bacteria as Mediators of Diet-Disease Relationships: Obesity and Inflammation and Cancer



- Bacterial endotoxin activates the immune system through gut epithelial Toll-like receptor 4.
- Endotoxin (LPS) may play a role in activation of immune cells in adipose tissue.



Effect of Cheeses on Gut Microbiome in Rodents

- Camembert and microbes from milk fermented with yogurt starters can survive intestinal transit
- Had a beneficial influence on intestinal metabolism
 - a decrease in azoreductase activity and NH₃ concentration
 - an increase in mucolytic activities.
 - the proportion of ursodeoxycholic resulting from chenodeoxycholic epimerisation was higher
 - β -galactosidases were higher
 - azoreductases and nitrate reductases were lower.
- Camembert feeding did not modify intestinal bacterial populations

Summary



- Limited evidence from human studies linking specific dairy products with cancer risk.
 - *Often evaluate dairy products generally, not specific products*
- Research from animal studies focus on effects of specific compounds
 - *Often fed at high doses*
 - *Relevance to human health?*
- Future research needs to study specific dairy products, taking into consideration the differences among products.