U.S. Regulation and Safety Assessment of Food-Contact Substances

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Today's Presentation

- Overview of major **U.S. laws** governing food additives and food-contact substances
- **Regulatory options** for premarket safety review of food-contact substances
- FDA **regulations** and approach to **safety assessment** of food-contact substances
- **Case study**

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Major U.S. Food Additive Laws

- **The Federal Food Drug and Cosmetic Act (FDC Act) of 1938** – giving FDA broad responsibilities to control use of food additives without pre-market clearance authority
- **Food Additive Amendment of 1958** – establishing **pre-market approval** system for direct and indirect food additives
- **Food and Drug Administration Modernization Act (FDAMA) of 1997** – establishing **Food Contact Notification** system for authorizing the safe use of food contact substances

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Food Additive Amendment of 1958

- **Definition of food additive** - "Any substance the intended of which results or reasonably expected to result – ***directly or indirectly*** – in its becoming a component …. To be safe under the **conditions of its intended use** ….."
- **Food additive petition process** -- All new food additives or new uses of regulated food additives subject to premarket review and approval by FDA

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General Safety Standards

- **Definition** – "Safety requires *proof of a* ***reasonable certainty*** that no harm will result ……. It ***does not*- and *cannot*-** require proof beyond any possible doubt that no harm ……"
- **Absolute safety** of any substance can **never be proven**.

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Delaney Anti-Cancer Clause

- General safety standards **inapplicable** to **carcinogenic** food additives
- Use of a food additive that ***has been shown to induce cancer in humans or animals upon oral ingestion*** *can not be approved*
- **No level of exposure** to a carcinogenic food additive can be considered safe under the **FDC Act**.

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Regulatory Options for Premarket Safety Review of FCS

- **Food Additive Petition** (FAP)
- **Threshold-of-Regulation** (TOR)
- **Food Contact Notification** (FCN)

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Food Additive Petition (FAP) Process

- Packaging material **not legal** until FDA publishes a **regulation** to permit its use
- Regulation written to be **generic**. Applicable to everyone who has the same product for the same use
- Regulation to be composed of 3 parts: identity of additive, chemical and physical specifications, and limitations on the conditions of its use
- Responsible for thousands of food-contact materials on FDA's **positive lists** – parts 175-179 of **21 CFR**

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21 CFR Parts 175-179

- **Part 175** – Adhesives and components of Coatings
- **Part 176** – Paper and paperboard components
- **Part 177** – Polymers
- **Part 178** – Adjuvants, production aids and sanitizers
- **Part 179** – Irradiation in the production, processing and handling of food

Note: Focus is on packaging components, not packaging constructions!

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Examples of Subparts

- Part 177 – Polymers
  - ***Subpart B*** – Substances for use as basic components of single and repeated use food-contact surfaces
  - ***Subpart C*** – Substances for use only as components of articles intended for repeated use

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Example of Section

- Part 177 -- Polymers
  Subpart B – Substances for use as basic components of single and repeated use food-contact surfaces
  Section 1520 – Olefin polymers

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Prior-Sanctioned Substances

21 CFR Part 181, Subpart B

- **Section 23** – Antimycotics (e.g. sorbic acid)
- **Section 24** – Antioxidants (e.g. BHA, BHT)
- **Section 27** – Plasticizers (e.g. dibutyl sebacate)
- **Section 28** – Release agents (e.g. oleamide)
- **Section 29** – Stabilizers (e.g. calcium oleate)
- **Section 30** – Substances used in the manufacture of paper and paperboard products used in food packaging (e.g. PEG 400)

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Threshold-of-Regulation (TOR) Exemption Process

- **Regulation listing exempted** for food-contact substances that meet TOR requirements (Part 170.39 in 21 CFR)
- **A faster process** than food additive petitions
- **Same information** as FAP or FCN for **same exposure** level

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TOR Criteria

- Estimated **consumer exposure** to the food- contact material not to exceed **0.5 ppb** in the daily diet
- **No evidence** that the material is **carcinogenic** in man or animal
- No **structural basis** for suspecting the material to be a carcinogen or potent toxin
- TOR exemptions listed on **FDA's website**:

  http://www.cfsan.fda.gov/~dms/opa-torx.html

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Recommended Information for a TOR Submission

- **Identity** and **composition**
- **Conditions of use** – temperature, type of food contact, repeated or single use, etc.
- Chemistry data needed by FDA to assess the **probable consumer exposure** to the additive or other migrating materials (e.g. impurities)
- Results of an analysis of the **existing toxicological information** on the additive and its impurities
- **Environmental** impact information

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Food Contact Notification (FCN) Process

- Authorized by Congress under the ***Food and Drug Administration Modernization Act of 1997***
- Began **operation** on October 22, 1999; **converting** then existing FAPs to FCNs
- Began **accepting** new notifications on January 18, 2000

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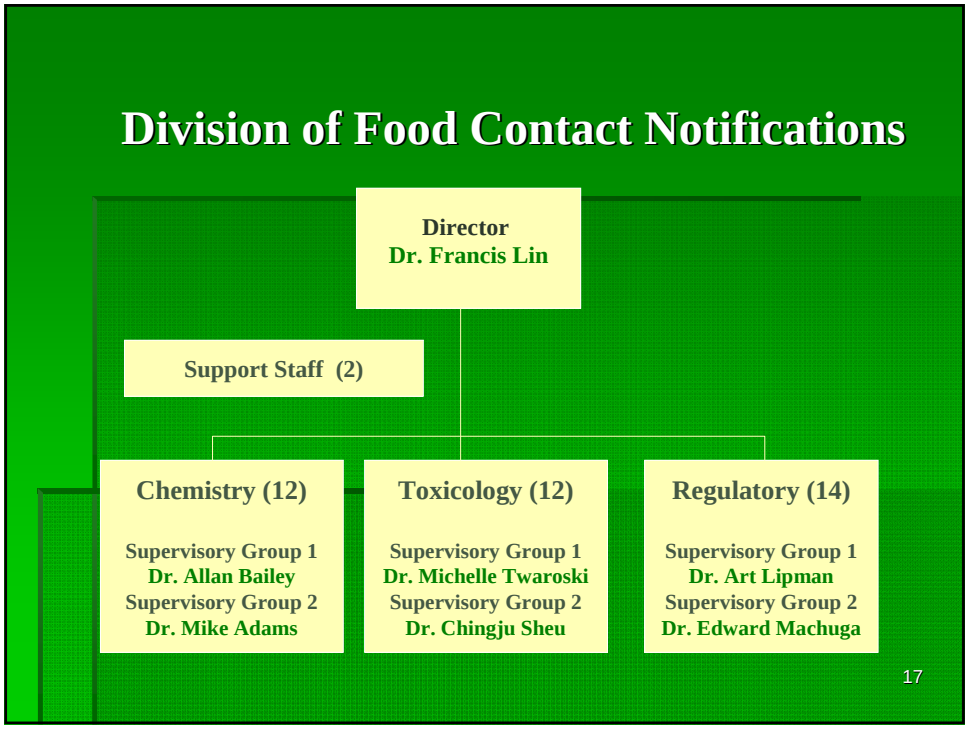
Division of Food Contact Notifications



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Definition of Food Contact Substance (FCS)

- **As defined in 1997 FDAMA** -- any substance intended for use as a **component** of materials used in manufacturing, packing, packaging, transporting, or holding food
- If such use is **not intended** to have a **technical effect** in food

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Definitional Coverage of FCS

- **Indirect Food Additives** --- Polymers, monomers, polymerization aids, adjuvants, equipment components, packaging compounds subject to irradiation
- **Some Secondary Direct Food Additives** -- boiler water additives, ion exchange resins, sugar processing additives, antimicrobials used in the processing of produces, vegetables, meats and poultries

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Current Inventory of FCN Program

(as of September 24, 2009)

- **Total FCNs 937**
- **Effective FCNs** 714
- **FCNs withdrawn** 195
- **FCNs not accepted** 8
- **FCNs currently under review** 22

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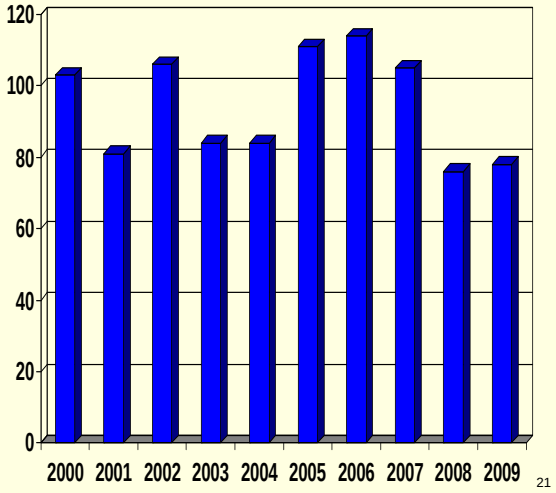
FCNs Received by FY

- FY 2000 103
- FY 2001 81
- FY 2002 106
- FY 2003 84
- FY 2004 84
- FY 2005 111
- FY 2006 114
- FY 2007 105
- FY 2008 76
- FY 2009 78



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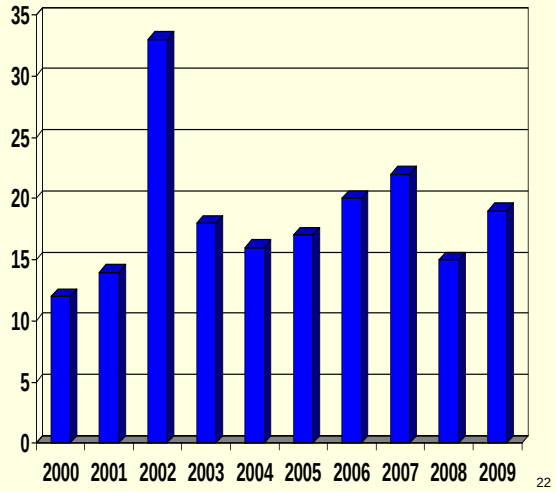
FCNs Withdrawn by FY

- FY 2000 12
- FY 2001 14
- FY 2002 33
- FY 2003 18
- FY 2004 16
- FY 2005 17
- FY 2006 20
- FY 2007 22
- FY 2008 15
- FY 2009 19



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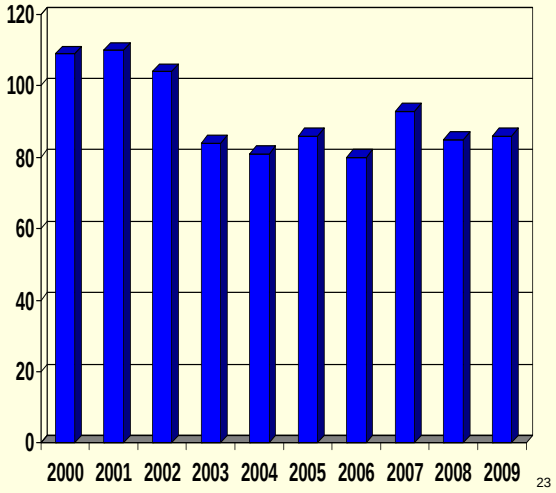
Days to Complete Review of FCNs by FY

FY 2000	109
FY 2001	110
FY 2002	104
FY 2003	84
FY 2004	81
FY 2005	86
FY 2006	80
FY 2007	93
FY 2008	85
FY 2009	86



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Information Needed to Support A Food Contact Notification

- **Identity** of the food-contact substance
- **Manufacturing** process, technical **effect**, and intended **conditions of use**
- The **notifier's determination** of safety
- Data and information that form the **basis** of the **safety determination**, and
- **Environmental** considerations

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FCN Process –
FDA Guidance Documents

1. **Administrative**
   http://www.cfsan.fda.gov/~dms/opa2pmna.html
2. **Chemistry**
   http://www.cfsan.fda.gov/~dms/opa2pmnc.html
3. **Toxicology**
   http://www.cfsan.fda.gov/~dms/opa2pmnt.html
4. **Environmental**
   http://www.cfsan.fda.gov/~dms/opa-guid.html

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FCN Process –
Pre-Notification Consultation (PNC)

- **Purpose** is to assist notifiers through the regulatory process. Uses of the process include:
  - Clarification on interpretation of regulatory status
  - Clarification on multiple FCNs
  - Request for CEDI, ADI, and UCR values
  - Pre-submission review of safety package
  - Discussion of alternative approaches to determining safety
- **Format** includes written and oral correspondence as well as meetings.

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Key Steps in FCN Review Process

- **Phase 1** review meeting within **3 weeks** from receipt of FCN
- **Acknowledgement letter** to notifier if the FCN is accepted at phase 1 meeting
- Notifier to **withdraw** the FCN if it is **not accepted** for further review
- **Phase 2** review of accepted FCN completed within **120 days**

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Key Steps in FCN Review Process (cont'd)

- **Final letter** to notifier if FDA does not object to the notification after phase 2 review
- **Effective FCNs** listed on FDA's website:

  http://vm.cfsan.fda.gov/~dms/opa-fcn.html

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Phase 1 Review of New FCNs

- A **critical component** of FDA's safety review process for food contact substances
- A **pre-acceptance screening** procedure
- **Purpose**: To determine, through a cursory review of the various components of a new submission, whether any **major deficiencies** or **obvious problems** exist which may affect the **acceptability** of the submission as a notification

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Data To Be Provided for Safety Evaluation

- **Chemistry data** for confirming identity of a food-contact substance and for assessing potential consumer exposure to the substance and its constituent impurities
- **Toxicology data** for use as basis for establishing a safe level of consumer exposure to the substance and its impurities
- **Chemistry and toxicology data** should be on substances **expected to migrate** to food under the intended conditions of use.

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Chemistry Information to be Provided in FCNs

- **Clear identification of the substance** -- chemical name, common name, trade names, CAS registry #, chemical structure and formula, molecular weight, spectroscopic data (IR, NMR, MS, etc.),
- **Details on manufacturing process** -- raw materials, catalyst, chemical reactions and reaction conditions, purification steps, chemical equations, potential migrants, etc.
- **Physical/chemical specifications** – physical appearance, melting points, density, solubility, glass transition temperature, molecular weight distribution, fraction of low molecular weight oligomers, impurity levels (especially carcinogenic contaminants).

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Chemistry Information (cont'd)

- **Clear description of the conditions of use for the substance** – proposed use, typical and maximum use levels, maximum thickness, single/repeat use applications, types of food to contact, maximum time and temperature conditions for food contact
- **Intended technical effect on the food-contact article** – technical data demonstrating the effect of substance at the minimum concentration

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Chemistry Information (cont'd)

- **Stability during the intended use or during migration testing** – describe occurrence of any chemical breakdown and alteration (oxidation, hydrolysis, etc.) and identify products from such occurence and provide their levels in the FCS. Need to provide supporting data.

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Chemistry Information (cont'd)

- Data from **migration studies** using food-simulating solvents
- Migration data used by FDA to assess potential **consumer exposure** to the substance
- **End test –** are not migration tests. They are compliance/quality control tests (e.g. 21 CFR 175.300, 176.170 and other sections in 21 CFR)

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Typical Migration Studies

- **Accelerated temperature/time conditions** intended to simulate thermal processing and extended storage
- Consistent with the intended conditions of use with respect to **use level, food types and temperatures**
- Use of food **simulating solvents** rather than real foods

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Food Simulating Solvents Recommended by FDA

- **10% ethanol** to model aqueous and acidic foods
- **10% or 50% ethanol** to model low- and high-alcoholic foods, respectively
- **Corn oil or synthetic fat** such as Miglyol to model fatty foods

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Temperatures/Times for Typical Migration Studies

- **Room temperature** – 40^0 C for 10 days
- Refrigerated food applications – 20^0 C for 10 days
- **Frozen food applications** – 20^0 C for 5 days
- **Boiling water sterilizing applications** – 110^0 C for 2 hours, then 40^0 C for 238 hours for a total of 10 days
- **High temperature, heat sterilized or retort above 100** – 121^0 C for 2 hours, then 40^0 C for 238 hours for a total of 10 days

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Alternatives to Migration Testing

- **100% migration calculation** – worst-case scenario, assuming 100% migration of FCS or its impurities to food; Examples: repeated use articles such as conveyer belts and food processing equipment
- **Diffusion theory calculation** – Fick's law and diffusion coefficients

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Exposure Assessment

- To estimate probable **consumer exposure** in terms of **concentration** (ppb or ppm) of the FCS in the **daily diet** or **Estimated Daily Intake** (EDI, mg/person/day) of the substance
- **Combine** migration levels determined from migration studies with **packaging information** on uses of food contact articles that contain the FCS

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Packaging Factors Used in Exposure Assessment

- **Consumption factor (CF)** – fraction of the daily diet expected to contact specific packaging materials **(e.g. 0.14 for polystyrene)**
- **Food-type distribution factor (f_t)** – fraction of all food contacting each material that is aqueous, acidic, alcoholic, or fatty **(e.g. 0.67 for aqueous food contacting polystyrene)**

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Concentration of FCS in the Daily Diet

- **Total migration of the FCS (<M>)** --

  $<M> = F_{\text{aqueous and acidic}} (M_{\text{10\%EtOH}}) + F_{\text{alcohol}} (M_{\text{50\%EtOH}}) + F_{\text{fatty}} (M_{\text{fatty}})$
- **Dietary concentration of migrant** –

  <M> x CF = ppb or ppm in the daily diet
- **EDI of migrant** = 3000 g food/person/day x dietary concentration of migrant

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Toxicology Data Recommendations

- Toxicology data needed for **establishing a safe level** of consumer exposure to an FCS
- The **greater** the expected **exposure**, the **more toxicity information** required to support safety
- **Exposure-driven** tiered approach recommended by FDA for safety testing
- **Toxicology guidelines** available on **FDA's website**:

  http://vm.cfsan.fda.gov/~dms/opa-pmnt.html

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Toxicity Tests for FCS with Dietary Exposure Less Than 0.5 ppb

- **No** toxicity tests needed
- Need to provide **literature search** on the FCS with focus on any reports concerning its **mutagenicity** and **carcinogenicity**

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Toxicity Tests for FCS with Exposure in 0.5 to 50 ppb Range

- **Short-term tests for genetic toxicity**
  - Gene mutation in bacteria, e.g. Ames test
  - In vitro cytogenetic test in mammalian cells, OR in vitro mouse lymphoma assay

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Toxicity Tests for FCS with Exposure in 50ppb to 1 ppm Range

- **Battery of three genetic toxicity tests**
  - ✓ Gene mutation in bacteria, e.g. Ames test
  - ✓ In vitro cytogenetic test OR in vitro mouse lymphoma assay
  - ✓ In vivo micronucleus test
- **Two 90-day subchronic studies,** one in a rodent species and the other in a non-rodent species
- **Additional studies**, as appropriate

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Toxicity Tests for FCS with Exposure Greater Than 1 ppm

- **Subchronic studies** in a rodent and a non-rodent species
- **Chronic (1-year) studies** in a rodent and a non-rodent species
- **2-year carcinogenicity bioassays** in 2 rodent species, with one including an in-utero exposure phase in its study design
- **2-generation reproductive study** in rats with a teratology phase
- **Other specialized studies**, as appropriate

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Acceptable Daily Intake (ADI)

- **"ADI** is an estimate of the amount of a chemical that can be ingested daily without appreciable health risk" by ***R. Walker, Fd. Add. Contam. Vol. 15, Supplement, 11-16, 1998.***
- Establish a **no-effect-level (NOEL)** for each toxic effect based on the study, species, strain and sex that appear to be most sensitive to the effect identified.
- Divide **NOEL** for each identified effect by an appropriate **safety factor**.
- The **lowest value** is the **ADI** for the **FCS**.

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Safety Factors

- Two **chronic** studies – **100**
- Rodent **AND** non-rodent **subchronic** studies – **1000**
- Rodent **OR** non-rodent **subchronic** studies – **2000**
- **Reproductive/teratology** studies – **100** for reversible effects and **1000** for irreversible effects

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Safety Determination of a Food Contact Substance

- A food-contact substance is **considered safe** for its intended use if the probable consumer exposure **(EDI)** to the substance is **less than** or **approximates** the Acceptable Daily Intake **(ADI).**

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Examples of Carcinogenic Constituents

- **Unreacted monomers** (e.g. vinyl chloride, ethylene oxide, acrylamide, 1,3-butadiene, acrylonitrile, epichlorohydrin**)**
- **Residual solvent** (e.g. methylene chloride, benzene, chloroform)
- **Manufacture side products** (e.g. 1,4-dioxane, 2,4-diaminotoluene)
- **Contaminating impurities** (e.g PAHs, PCBs, TCDD)

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Carcinogenic Risk Assessment

- **Calculation of Unit Cancer Risk (UCR)** – Defined as ***the sum of the slopes of lines drawn from the lowest effective dose of the constituent through zero for each tumor site in a bioassay***
- **The upper bound lifetime cancer risk** – multiplying the UCR by the estimated daily intake (EDI) of the constituent
- In general, trace levels of a carcinogenic contaminant in food are **tolerable if the risk is less than 1 x 10^{-6}**.

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Phase I SAR Analysis

- **Structure-Activity Relationship (SAR)** analysis helps answering questions:
  (1) Does the chemical contain structural alerts?
  (2) Do we have experience with the chemical?
- Analyzing FCS and impurities using **"expert" systems** (e.g. OncoLogic and MultiCASE) and FDA's **internal databases**
- **Qualitative** in nature: low, moderate, high level of concern

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Phase II SAR Analysis

- Using **quantitative SAR** (QSAR) approach to estimate risk to chemicals with **structural concerns** or **non-negative** mutagenicity data
- Identifying **chemical analogs** in the Handbook of Carcinogenic Potency and Genotoxicity Database of FDA's own databases
- Using the **TD_{50}** values or **UCRs** to calculate an estimate of upper bound cancer risk for the **chemical of interest**

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Safety Evaluation of Food Contact Substances

A Case Study

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Identity of FCS

- **2,2-methylenebis(4,6-di-tert-butylphenyl)-2-ethylhexyl phosphite**
- CAS # 126050-54-2
- MW: 582.9 g/mole
- Purity: over 99%

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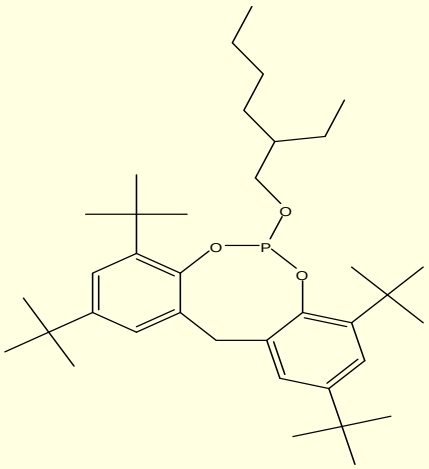

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Use and Intended Technical Effect

Intended for use as an antioxidant in:

- PP at 0.25 wt% or less
- HEDP at 0.15 wt% or less
- LLDPE at 0.15 wt% or less

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Food Types and Conditions of Use

- **PP, HDPE and LLDPE** –
  - Aqueous, acidic and dry food under use conditions B-H
  - Alcoholic and fatty foods under use conditions C-G

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Migration Studies on FCS-Containing PP

- Studies done on **PP strips** containing 0.25 wt% of the additive
- 10% ethanol – 100 C for 2 hours then 49 C for 10 days **(aqueous and acidic food)**
- 50% ethanol – 81 C for 2 hours then 49 C for 10 days **(alcoholic food)**
- 95% ethanol – 71 C for 2 hours then 49 C for 10 days **(fatty food)**

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FCS Exposure Based on Migration Study on PP

- 10-day migration values from the migration experiment were used
- Concentration of additive in food contacting PP:

$<M> = (f_{aq} + f_{ac})(M_{8\%al}) + (f_{al})(M_{50\%al}) + (f_{fatty})(M_{95\%al})$

$= (0.67 + 0.01)(0.067 \text{ ppm}) + (0.01)(0.59 \text{ ppm}) + (0.31)(2.05 \text{ ppm})$

$= \mathbf{0.69 \text{ ppm}}$

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FCS Exposure (cont'd)

- Assuming a minimum **consumption factor (CF)** of 0.05 for PP
- **Dietary concentration** of the additive

= CF x <M> = (0.05)(0.69 ppm)

= 0.035 ppm or **35 ppb** in the daily diet

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FCS Exposures Based on Migration Studies on Other Polymers

- Additive exposure from HDPE – 135 ppb in the daily diet
- Additive exposure from LLDPE – 80 ppb
- **Cumulative dietary exposure to the additive from its use in PP, HDPE and LLDPE : 35 + 135 + 80 =250 ppb (or 0.75 mg/person/day)**

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Safety Data on the FCS

- **Acute oral toxicity study in rats** – greater than 5000 mg/kg bw
- **Bacterial mutagenicity (Ames) tests** – negative in the absence or presence of exogeneous metabolic activation
- **Short-term (4-week) dietary study in rats –**
  - Sprague-Dawley, 15/sex/group
  - 0, 400, 200, 10000 and 50000 ppm in the diet for 4 weeks
  - Minimal effects on body wt gain at 50000 ppm

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Safety Data (cont'd)

Subchronic (3 months) oral toxicity study in rats –

- Sprague-Dawley rats, 20/sex/group
- 0,500, 5000 and 50000 ppm in diet for 90 days
- **Clinical observations and mortality** – not remarkable
- **Body weight gains** – not effected at all dose levels
- **Food consumption** – increased at 50000 ppm
- **Clinical laboratory data (blood chemistry, hematology, urinalysis and ophthalmological exam)** – no treatment-related changes

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Safety Data (cont'd)

- **Absolute and relative organ weights** – no treatment-related changes
- **Gross pathology** – not remarkable
- **Histopathology** – not remarkable
- **No-effect level (NOEL)** set at the highest dose level of 50000 ppm (**actual intake of additive – 4600 mg/kg/bw).**

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Safety Evaluation of FCS

- Applying a **safety factor of 2000** to the NOEL for lack of a non-rodent subchronic study
- **Acceptable Daily Intake (ADI)** = 2.3 mg/kg/day or 138 mg/person/day
- **EDI** (0.75 mg/person/day) **< ADI** (138 mg/person/day)
- ***Conclusion: The additive is safe for its intended use as an antioxidant in PP, HDPE and LLDPE***

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Thank you for Your Time and Attention!

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