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Similarities and Differences in Technical Reviews of Color Additives by the U.S. FDA, EFSA, and JECFA

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Reviews of Color Additives

- Technical reviews for color additives are not all the same across jurisdictions
  - U.S. Food and Drug Administration (FDA)
  - European Commission (EC) & European Food Safety Authority (EFSA)
  - Joint FAO/WHO Expert Committee on Food Additives (JECFA)

- For discussion today
  - Regulatory frameworks / process
  - Data requirements
  - Data interpretation / risk assessment
  - Some examples

United States (U.S.)

- Under the Federal Food, Drug, and Cosmetic Act (Chapter VII, section 721), color additives are subject to FDA approval before they may be used in food, drugs, or cosmetics, or in medical devices; approved color additives are listed in 21 CFR
- An interested person may petition the FDA for the proposed use of a color additive and submit data demonstrating its safety and suitability as described in 21 CFR Part 71
- Color Additive Petition (CAP):
  - FDA reviews the petition
  - Color additive regulations at 21 CFR 70.3(i) define "safe" to mean that there is convincing evidence establishing with reasonable certainty that no harm will result from the intended use of the color additive
  - No set clock for the review; "the approval process varies significantly" for CAP
  - FDA encourages consultations prior to submission of a CAP

European Union (EU)

- Regulation (EC) No 1331/2008 establishes the common authorization procedure for food additives, food enzymes and food flavorings
- Colors added to foods are regulated as food additives under Regulation (EC) No 1333/2008; authorized food additives are presented in order of E-number
- An interested person may submit an application to the European Commission requesting use of a color additive
  - Safety needs to be considered by independent scientific experts to determine the acceptable amount of the additive that can be included in the diet
  - Risk assessment is undertaken by EFSA - the expert Panel on Food Additives and Flavorings (FAF)
  - Set “clocks” exist for phases of the review, though the clock stops between steps
  - No consultations prior to submission

JECFA

- Only food additives listed in the General Standard for Food Additives (GSFA) may be used
- Process for an additive to be included in the GSFA begins with a JECFA evaluation
- JECFA issues a Circular Letter (CL) requesting proposals for substances to be added to the JECFA priority list for evaluation. A company, through a government, or through an NGO and then supported by a government, requests that its additive be added the JECFA priority list
- The company submits a dossier to JECFA
  - WHO Experts (monographers) prepare monographs for JECFA and Members (reviewers) are assigned to peer review the monographs
  - Discussions occur at specified meeting dates; timing to complete review is variable
  - No consultations prior to submission

General Data Requirements in All Submissions

- Chemical and technological data
- Dietary exposure assessment
- Toxicological data

Chemical and Technological Data

Required Data Element	U.S. FDA	EFSA	JECFA
Identity • Name • Chemical formula, molecular structure, IUPAC/CAS RN • Description of source • Description of chemical, physical, and biological tests for establishing identity • Compositional data	Yes	Yes	Yes
Physical and chemical properties • Chemical, spectroscopic and chromatographic analyses	Yes	Yes	Yes
• Solubility • Particle size determination • Influence of pH on solubility – ionisation constant(s) • Octanol / water partition ratio	-	Yes	-

Chemical and Technological Data, con't

Required Data Element	U.S. FDA	EFSA	JECFA
Specifications	Yes	Yes	JECFA develops the specifications based on proposed specifications in the submission; applied during development and toxicological studies
Certificates of analysis	≥ 5 non-consecutive batches	5 independent batches	≥ 5 batches

Chemical and Technological Data, con't

Required Data Element	U.S. FDA	EFSA	JECFA
Manufacturing process description	Yes	Yes	Yes
Stability data -Stability of the colorant in storage -Stability in food	Yes	Yes	
Analytical methods for -Enforcing specifications -Detection in food and identification of substances formed in food as a result of use	Yes	Yes	analytical techniques for identifying and quantifying the listed substances
Proposed uses and limitations	Yes	Yes	Yes
Labelling	Yes		
Sample for testing	Maybe		

Chemical Specifications – Typical Parameters

Parameter	Description
Characteristics	Appearance Density pH Brix Solubility Spectrophotometry HPLC Infrared spectrum
Purity	Loss on drying Water insoluble matter Ether-extractable matter Impurities Heavy metals Microbiological contaminants Pesticide residues

Estimated Daily Intake of Substance

$$EDI = food\ consumption\ x\ \%\ use\ in\ food$$

- Use level assumed in each food category
- Sum intake across all proposed uses in food
- Data
  - Dietary recall data
  - Model diets
  - Budget method - provides conservatively high estimate of intake

Refined Estimated Daily Intake of Substance

$$EDI = food\ consumption\ x\ \%\ use\ in\ food$$

$$x\ \%\ of\ food\ colored$$

$$x\ \%\ of\ foods\ that\ are\ specific\ color\ [blue]$$

- Food composition data used to identify % of food colored (e.g., candy shell or other coating)
- Market share data used to identify proportion of colored foods that are a certain color (Mintel Label Database, representative product data)

Dietary Exposure Assessments by Review

Component	U.S. FDA	EFSA	JECFA
Food categories	21 CFR 170.3(n)	Food categories in Part E of Annex II to Regulation (EC) No 1333/2008 on Food Additives	General Standards for Food Additives (GSFA)
Consumption data	What We Eat in America / National Health and Nutrition Examination Survey (WWEIA NHANES)	1st tier assessment: Food Additives Intake Model (FAIM) exposure assessment tool 2nd tier assessment: DietEx tool - EFSA Comprehensive Food Consumption Survey database	Global: The Americas [US, Brazil], Europe, Asia, Africa (Model Diets: EFSA Comprehensive Database and FAO/WHO Chronic Individual Food Consumption summary statistics [CIFOCOss] Database)
Age groups	2+, toddlers, children, adolescents, adults, and elderly	Infants, toddlers, children, adolescents, adults, and elderly	Infants, toddlers, children, adolescents, adults, and elderly
Use level	Maximum	Typical & Maximum	Typical & Maximum
Upper percentile consumers	90th percentile	95th percentile	95th percentile
Main food contributing to dietary exposure	No	Yes	Depends on the reviewer
Refined assessment	Yes	Yes	Yes, also “brand-loyal” scenario

Dietary Exposure Assessment Lessons Learned

- When anticipating approvals across jurisdictions
  - Crosswalk food categories targeted for color additive use
  - Assume consistent use levels across jurisdictions, if possible
- Plan for refinement with country/region-specific market share data
- Highest exposures on a bodyweight basis are typically populations of children; allow for exposure in “brand-loyal” scenarios for exposure by children to remain below the acceptable daily intake

Framework for Required Safety Data

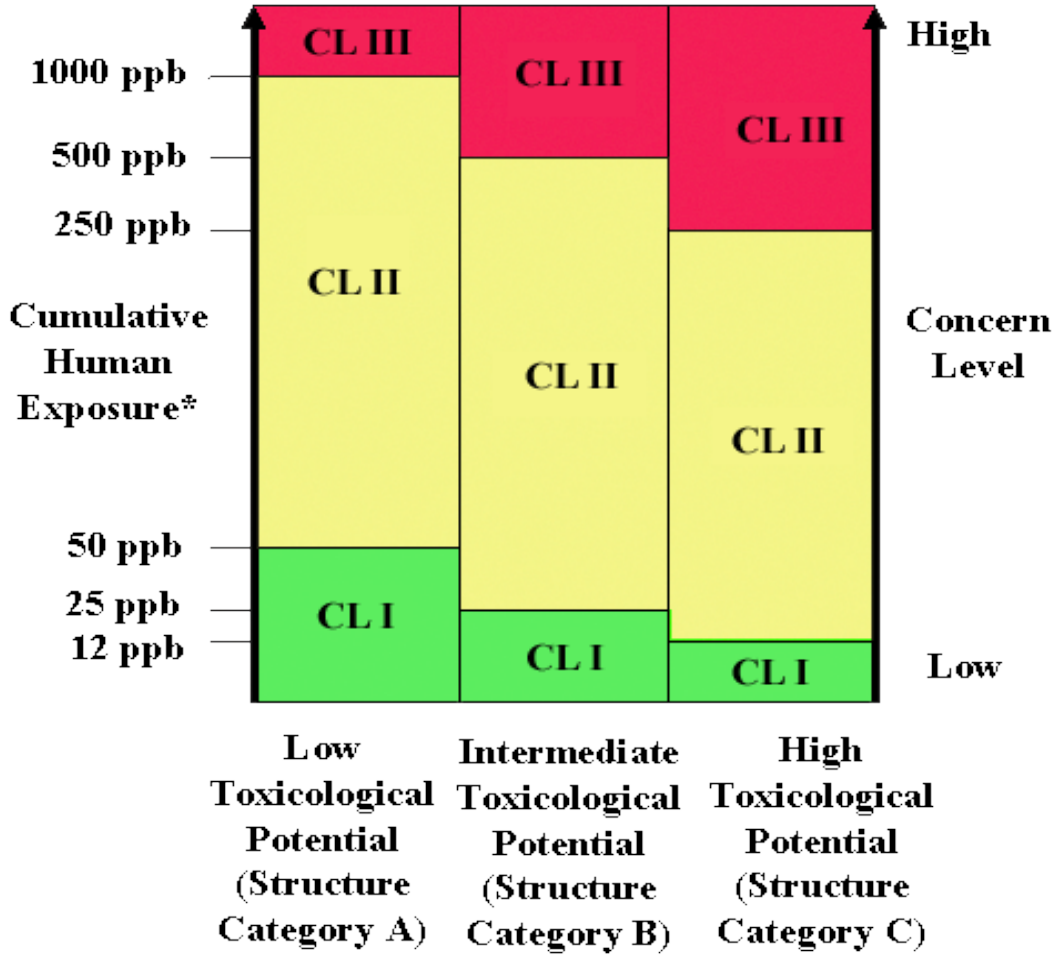
U.S. FDA	EFSA	JECFA
Based on Concern Level (CL) - reflection of additive's toxicological potential predicated from chemical structure and estimation of cumulative human exposure (FDA Redbook II)	Tiered approach	*Principles and methods for the risk assessment of chemicals in food* – Environmental Health Criteria No. 240

U.S. FDA - Toxicological Data for Food Additives

- FDA provides guidance concerning procedures and safety assessment of food and color additives
- “Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Foods”
  - Known as the “Redbook”
  - First published in 1982, updated periodically since

Redbook: Concern Levels (CL) as Related to Human Exposure and Chemical Structure

- Additive is placed in one of three broad categories based on information about the additive's structure (toxicological potential)
- Cumulative human exposure of daily dietary consumption of additive
  - In diet as ppb, or divide ppb in diet by 20 to convert to mcg/kg bw/day
  - e.g., 600 ppb in diet = 30 mcg/kg bw/day
- Human exposure determines the initial Concern Level to which the additive is assigned
- Exposure information frequently has more weight than structure alert information in assigning additives to a Concern Level
- If available, other information may be considered when setting the Concern Level, and final safety decisions are made on a case-by-case basis



Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-summary-table-recommended-toxicological-testing-additives-used-food

Redbook: Recommended Toxicological Testing Summary for Additives Used in Food

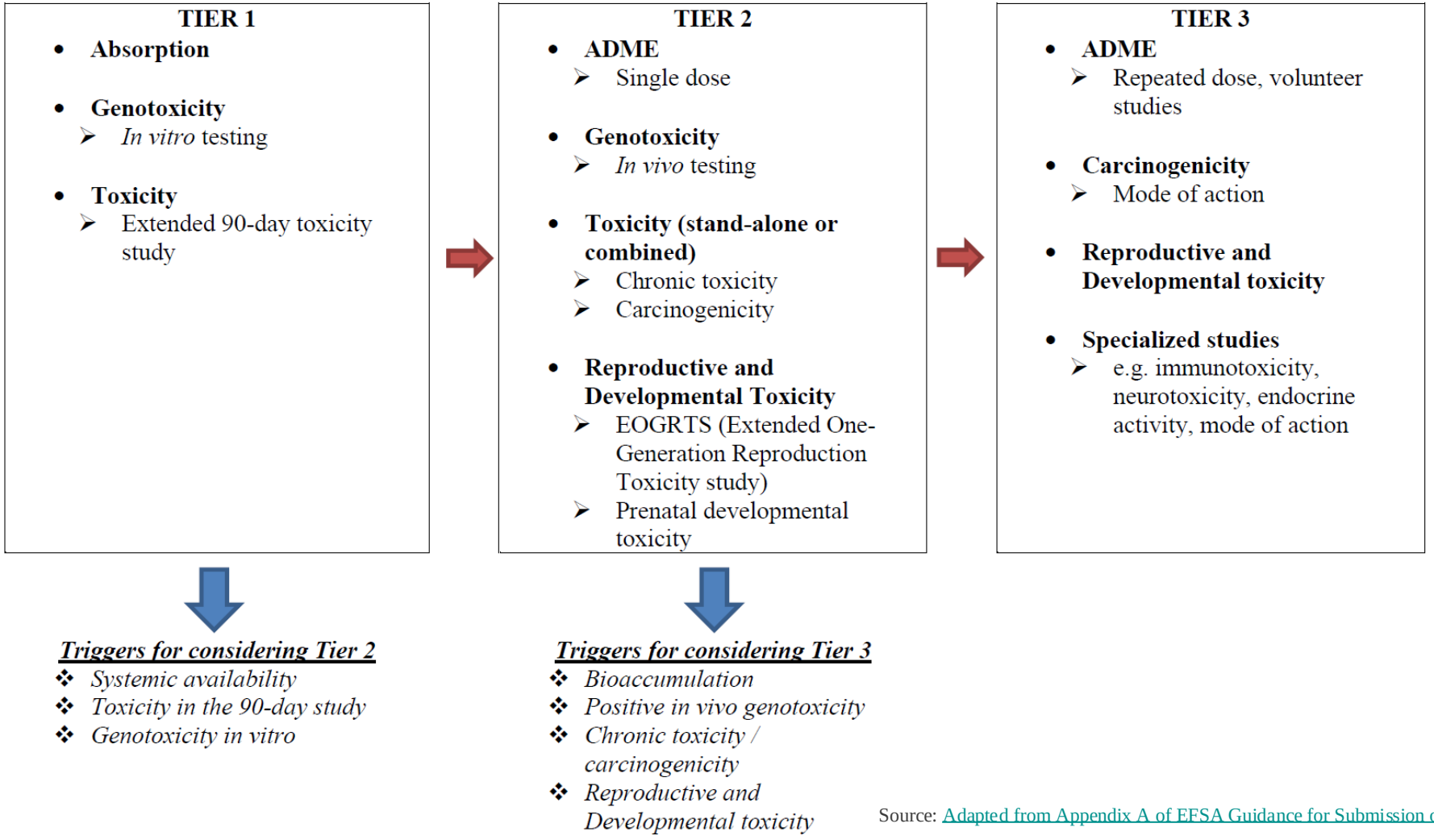
Toxicity Tests	Concern Level Low (I)	Level Intermediate (II)	Concern Level High (III)
Genetic toxicity tests	X	X	X
Short-term toxicity tests with rodents	X[c]	X[a,c]	X[a,c]
Subchronic toxicity studies with rodents		X[c]	X[a,c]
Subchronic toxicity studies with non-rodents		X[c]	X[a,c]
One-year toxicity studies with non-rodents			X[c]
Chronic toxicity or combined chronic toxicity/carcinogenicity studies with rodents			X[c]
Carcinogenicity studies with rodents			X
Reproduction studies		X[c]	X[c]
Developmental toxicity studies		X[b,c]	X[b,c]
Metabolism and pharmacokinetic studies		X[b]	X[b]
Human studies			X[b]

a. If needed as preliminary to further study
b. If indicated by available data or information
c. Including screens for neurotoxicity and immunotoxicity

EFSA - Toxicological Data for Food Additives

- As a general principle, a tiered approach to toxicological evaluation should be adopted which balances data requirements against the risk
- Framework consists of 3 tiers of testing:
  - Tier 1: Minimal dataset applicable to all compounds
  - Tier 2: More extensive data required for compounds which are absorbed and/or demonstrate (geno)toxicity in Tier 1 tests
  - Tier 3: Testing performed on a case-by-case basis, elucidate specific endpoints needing further investigation of findings in Tier 2 tests
- Testing conducted in compliance with OECD guidelines / GLP

Summary of EU Tiered Toxicology Testing Approach for Food Additives



Source: Adapted from Appendix A of EFSA Guidance for Submission of Food Additive Evaluations

Toxicological Approach for JECFA Review

- Procedures for the evaluation of chemicals in food as outlined in *Principles and Methods for the Risk Assessment of Chemicals in Food* – Environmental Health Criteria No. 240; a risk assessment approach
- Data considered:
  - Metabolism and pharmacokinetic studies
  - Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity and developmental toxicity studies in animals, genotoxicity studies;
  - Epidemiological studies; and
  - Special studies designed to investigate specific effects, such as the mechanism of toxicity, immune responses, or macromolecular binding

Toxicological Data & the Safety Assessment

- Toxicological data needs and interpretation can vary across jurisdictions
  - U.S. FDA Redbook Concern Levels and case-by-case guidance vs
  - EFSA's tiered approach vs
  - JECFA review team
- Potentially different interpretation of findings from the same study
- The same data package does not necessarily result in the same interpretation and final risk assessment

Jagua (genipin-glycine) Blue (INS 183)

- Jagua (genipin-glycine) blue; principal coloring component is a genipin-glycine polymer
- Evaluations completed by JECFA (2020) and U.S. FDA (2023)
- Pivotal toxicological study:
  - 12-month repeated dose toxicity study including *in utero* exposure in rats
  - On the absence of treatment-related long-term toxicity or reproductive and developmental toxicity, **NOAEL identified as 1127 mg/kg bw/day** on a blue-polymer basis, the highest dose tested

Jagua Blue: JECFA vs U.S. FDA

JECFA

- High-level dietary exposure = 11.5 mg/kg bw/day, “brand-loyal” estimate
- Uncertainty Factor of 100 applied to the NOAEL (1,127 mg/kg bw/day)
- Committee noted that although no new toxicokinetic study was available, newly developed analytical methods for the dimers provided acceptable characterization of the test article, thus reducing uncertainty of the safety assessment due to limited biochemical information
- **ADI = 0-11 mg/kg bw/day on a blue-polymer basis**

Safety evaluation of certain food additives (Eighty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives) WHO food additives series No. 80, 2022.

U.S. FDA

- Highest dietary exposure = 138 mg/day (2.3 mg/kg bw/day), refined exposure assessment
- Uncertainty Factor of 500 applied to the NOAEL (1,127 mg/kg bw/day)
- Additional 5x factor applied for lack of metabolism and pharmacokinetics and long-term chronic study
- **ADI = 2.3 mg/kg bw/day on a blue-polymer basis or 138 mg/day**


DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. FDA–2020–C–2131]

Listing of Color Additives Exempt From Certification; Jagua (Genipin-Glycine) Blue

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

75490 Federal Register / Vol. 88, No. 212 / Friday, November 3, 2023 / Rules and Reg

Spirulina Extract (INS 134)

- Filtered aqueous extraction of dried biomass of *Arthrospira platensis*; phycocyanins are principal coloring component
- Multiple dietary sources of phycocyanins from spirulina products
  - Food color
  - Food ingredient
  - Dietary supplement and dietary supplement coating
- Evidence base includes data from studies of dried spirulina and spirulina extract
- Multiple evaluations completed by JECFA and U.S. FDA
- In the EU, spirulina is typically considered a coloring food (not a color additive)

Spirulina Extract: JECFA vs U.S. FDA

JECFA

- Dietary exposure of phycocyanins = 190 mg/kg bw/day for adults and 650 mg/kg bw/day for children, based on budget method for food color + other sources
- Based on absence of toxicity in repeated-dose studies with spirulina extract and dried spirulina, including short-term toxicity studies in mice (up to 45 000 mg/kg bw/day) and rats (up to 30 000 mg/kg bw/day) fed dried spirulina (4500 and 3000 mg/kg bw/day phycocyanins); no evidence of carcinogenicity or systemic toxicity in long-term toxicity studies in rats; no concerns regarding genotoxicity; reproductive and developmental toxicity not of concern based on absence of toxicity in feeding studies
- **ADI = "not specified" for spirulina extract**

95th JECFA - Chemical and Technical Assessment (CTA), 2022
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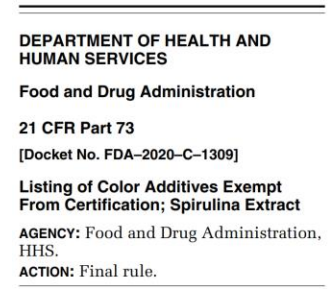
SPIRULINA EXTRACT

U.S. FDA

- Highest cumulative estimated dietary intake (CEDI) = 1.14 g/day phycocyanins (19 mg/kg bw/day for a 60 kg bw)
- Pivotal safety study: 21-month chronic oral rat toxicity study (Chamorro et al., 1988), NOEL supports No-Effect range for phycocyanin of 1.8-3.0 g/kg bw/day *or* 108-180 g/day
- Uncertainty Factor of 100 applied to the NOEL
- FDA Concluded there was an adequate margin of safety between the NOEL and CEDI for phycocyanins
- **ADI = 1.0-1.8 g/day phycocyanins**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. FDA–2020–C–1309]

Listing of Color Additives Exempt From Certification; Spirulina Extract

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

Federal Register / Vol. 87, No. 217 / Thursday, November 10, 2022

Summary Observations

- Regulatory frameworks and technical reviews for color additives are not all the same across jurisdictions
- Each data package and review will be unique
- There is a wide range of perspectives in the reviewers from each jurisdiction
- Different conclusions can be reached by different jurisdictions reviewing the same body of information

Thank you

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and thanks to my colleagues

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