1101 17th Street, NW • Suite 700 • Washington, DC 20036
T: 202-293-5800 E: info@iacmcolor.org
www.iacmcolor.org

March 8, 2016

National Bureau of Agricultural Commodity and Food Standards (ACFS)
50 Phaholyothin Road, Ladyao
Chatuchak, Bangkok 10900
Thailand
via E-mail: spsthailand@gmail.com

Re: WTO Notification G/SPS/N/THA/234

To whom it may concern:

The International Association of Color Manufacturers (IACM) is the trade association that represents the manufacturers and end-users of coloring substances that are used in foods globally, including natural and synthetic colors. We are writing to offer further information and express our concerns with some aspects of the recent proposal "The Notification of the Ministry of Public Health Regarding Food Additives No. 4, (Notification No. 4)". Specifically, we express concern with the proposed revisions to maximum levels (MLs) for certain food colors as well as the revision to Clause 2.

The proposal offers ML revisions for 10 food colors, and five of these in particular are concerning to color and food manufacturers in IACM's membership: Grape skin extract (INS 163(ii)); Caramel III - ammonia caramel (INS 150c); Caramel IV – sulfite ammonia caramel (INS 150d); Iron oxides (INS 172 (i)-(iii))[1]; and Riboflavins (INS 101 (i)-(iii)). IACM would strongly encourage that Thailand, at a minimum, adopt the current CODEX levels for these additives. Furthermore, specific to the use of iron oxides in foods, IACM wishes to inform you that the FDA recently amended the food color regulations (21 CFR 73.200) to provide for the expanded safe use of synthetic iron oxide as a color additive to include use in soft and hard candy, mints and chewing gum at levels consistent with GMP (i.e. no use limits) after considering available safety studies.[1]

The Thai FDA's Food Technical Subcommittee on Food Additives contends that exposure levels in Thailand are higher "based on Thailand's evaluation of actual food consumption data." While we acknowledge that Thailand attempts to establish lower MLs than those established by CODEX for food additives in various food groups to ensure that the intake of a food additive from all its uses does not exceed its ADI, IACM would contend that the rationale for doing so is not scientifically justified. IACM notes that, if indeed observed, higher intakes may be exceptional, infrequent, and not representative of the population of Thailand as a whole, and

[1] Please see recent US FDA tox review of iron oxides included as an addendum for further support.

therefore cannot be the basis for generalized regulatory actions. More importantly, exposure estimates based on the assumption of additive exposure at MLs is purely theoretical and highly improbable, such as the assumption that the additive is present at the ML in *all* the foods where it is allowed and an individual consumes *all* foods that contain this additive on a *daily* basis. These overly conservative assumptions bear little relevance to realistic exposure scenarios. The inaccuracy of this method is recognized by scientific committees worldwide and alternative more realistic exposure assessment methods have been developed to properly assess population exposure.[2]

IACM also has strong concerns with the proposal to modify Clause 2, currently stating "*where two or more food additives from the same functional class may be added to a food, the maximum permitted level after combination shall not exceed the permitted maximum level of the food additive that has the lowest tolerance*" to the proposed statement "*For the combined use of two or more food additives classified in the same functional class and where the maximum levels of each have been individually set, Notification No. 4 proposes that the sum of the proportions of each additive used cannot exceed one.*"

While the current clause already lacks a scientific basis, the proposed revision is even further scientifically unjustifiable because it is not consistent with the toxicological principles of dose or response additivity. The criterion proposed for considering additives with the same technological function as having equivalent or additive toxicological properties is not scientifically justified unless they share the same mode of action (ATSDR 2004).

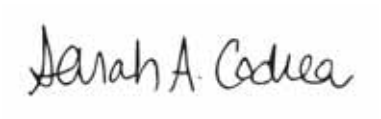
The principles of additive or synergistic toxicological effects require that substances be considered on the basis of their chemical structure or class, metabolic fate, and more importantly the mode of action in assessing additive toxicity and establishing combined exposure limits (US EPA 1986; 2000). Additives must be evaluated on an individual basis to determine safety, unless scientific justification indicates otherwise.

It is on the basis of these principles that neither CODEX nor any other food safety authority considers additives with the same technological function in a certain food together when evaluating exposure and developing an ADI. The same scientific justification guides exposure assessment methods in the US, Canada and the European Union.

We remain at your disposal to provide any additional information concerning the scientific justification behind development of appropriate exposure assessments and subsequent determination of maximum levels. We strongly urge that the scientific evidence informing maximum levels for these and all food colors be considered in a manner consistent with other government bodies and harmonized international standards. IACM thanks you for considering these comments.

Sincerely,

[2] Examples of scientifically validated exposure assessment methods contained as references to this letter.



Sarah Codrea
Executive Director

References

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United States Environmental Protection Agency (US EPA) (2000) Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. Risk Assessment Forum Technical Panel. EPA/630/R-00/002. Available online: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533&CFID=60708395&CFTOKEN=37676245

Memorandum

Date: 09/09/2014

From: T. Scott Thurmond, Ph.D., OFAS/DPR, Toxicology Team _____

Subject: Toxicology review of safety assessment information contained in CAP 3C0298, "Use of iron oxides as colorants in hard and soft candy, chewing gum, and pressed mints in amounts consistent with GMP."

To: Laura Dye, M.S., OFAS/DPR, Regulatory Team 2

Through: Catherine Whiteside, Ph.D., OFAS/DPR, Toxicology Team Supervisor_____

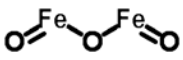
Related petitions: CAP 0C0228 (iron oxides as colorants in sausage casings) (21 CFR 73.200), CAP 51 (iron oxides in dog and cat food) (21 CFR 73.200)

Introduction:

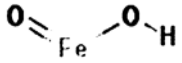
The Wm. Wrigley Jr. Company, through its agent, Exponent Inc. (1150 Connecticut Ave., NW, Suite 1100, Washington, DC 20036), has submitted a color additive petition (CAP 3CO298) seeking approval for the use of synthetic iron oxides (red, yellow, black) as colorants in sugar-sweetened and sugar-free hard and soft candies, pressed mints and chewing gum. While the Petitioner did not include new toxicity studies in their safety assessment package, they did include a review of published safety literature for iron oxides from 01/2001 to 02/2013, along with a summary of their review and copies of a number of articles found during that review. They also cited extensively from a review of safety information for a number of vitamins and minerals, including iron, found in the 2001 Institute of Medicine publication on reference intakes for these substances. In this evaluation DPR Toxicology will focus primarily on iron oxide-related safety articles the petitioner cited that were published subsequent to the IOM report. We will also evaluate any relevant papers that were published following the receipt of this petition.

Chemistry:

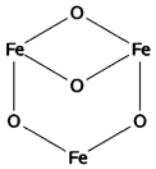
Iron Oxide Red (Fe_2O_3)
Synonyms: Synthetic hematite, CI Pigment Red 101 and 102, INS No. 172(ii)
CASRN: 1309-37-1
Mol. wgt.: 159.70



Iron Oxide Yellow ($FeO(OH)•xH_2O$)
Synonyms: Synthetic geoethite, CI Pigment Yellow 42 and 43, INS No. 172(iii)
CASRN: 51274-00-1
Mol. wgt.: 88.85



Iron Oxide Black ($FeO•Fe_2O_3$)
Synonyms: Synthetic magnetite, CI Pigment Black 11, INS No. 172(i)
CASRN: 1317-61-9
Mol. wgt.: 231.55



Exposure

DPR Chemistry estimated the dietary exposure to total and bioavailable iron (using a conservative bioavailability of 1% for iron oxides) for the U.S. population (aged 2+ years) from the petitioned use, as well as a cumulative estimated daily intake (CEDI) for total and bioavailable iron from all uses (Table 1., adapted from D. Doell chemistry memorandum of 06/20/2014). This reviewer has added the recommendations from the Institute of Medicine (IOM, 2001) for the Tolerable Upper Limit (UL) for total iron intake for the various age groups.

Table 1.

Summary: Exposure to Iron for the U.S. Population						**IOM UL Recommendations for Total Iron (mg/day)[1]**
		Total Iron (mg/p/d)		**Bioavailable Iron (mg/p/d)**		
	% Eaters	**Mean**	**90th Percentile**	**Mean**	**90th Percentile**	
Petitioned Use of Iron Oxides	29	6.8	16.3	0.07	0.16	
Children 2-5 years	100	18.4	31.2	2.70	4.68	40
Children 2-13 years	100	20.3	34.6	2.97	4.99	40
Adolescents/Adults 14+ years	100	23.3	41.5	3.58	6.21	45
CEDI (Regulated and Petitioned Uses, Dietary Sources and Dietary Supplements) 2+ years	100	22.8	40.6	3.48	6.02	

DPR Chemistry also provided exposure information for heavy metal contaminants from the proposed uses of iron oxides (Table 2., excerpted from D. Doell chemistry memorandum of 06/20/2014). Since the petitioner did not provide an exposure estimate for the contaminants, Chemistry provided a worst-case exposure for these heavy metals by presuming that they are present in iron oxides using the specifications proposed by the Petitioner (Arsenic, not more than 3 mg/kg; Lead, not more than 5 mg/kg; Mercury, not more than 1 mg/kg).

Table 2.

Eaters-Only Exposure to Arsenic, Lead, and Mercury from the Proposed Use of Iron Oxides							
Population	**% Eaters**	**Arsenic**		**Lead**		**Mercury**	
		Mean (µg/p/d)	**90th Percentile (µg/p/d)**	**Mean (µg/p/d)**	**90th Percentile (µg/p/d)**	**Mean (µg/p/d)**	**90th Percentile (µg/p/d)**
U.S. Population aged 2+ years	29	0.03	0.07	0.05	0.11	0.01	0.02
Children 2-5 years	46	0.02	0.05	0.04	0.09	0.01	0.02
Children 2-13 years	44	0.03	0.06	0.05	0.11	0.01	0.02
Adolescents/Adults 14+ years	26	0.03	0.07	0.05	0.11	0.01	0.02

Safety Evaluation of Iron Oxide:

[1] In calculating their UL, the IOM used an Uncertainty Factor (UF) of 1.5 to extrapolate from the Lowest Observed Adverse Effect Level (gastric irritation at 70 mg/day iron) to the No Observed Adverse Effect Level. This UF should not be considered as comparable to the safety factors used when extrapolating from animals to humans in safety assessment studies.

In their safety narrative, the petitioner cited a number of publications from the IOM 2001 iron Dietary Reference Intake literature review that dealt with the maintenance of normal heme and non-heme (ferrous) iron homeostasis in humans (it should be noted that the IOM report did not address iron oxides as possible dietary sources of iron). The Petitioner also discussed more recent publications (subsequent to the 2001 IOM Report) that they found in their own search that also addressed normal iron homeostasis. There were other publications on iron physiology, as well as discussions on normal iron homeostasis that were submitted as part of the safety data for iron oxide. This Reviewer considered these publications and discussions as general toxicology information for iron and to provide only supplemental information on the safety assessment of iron oxides. This information will not be reviewed in this evaluation of the safety of iron oxide.

Absorption of iron oxide

One of the main focuses of the petitioner's safety narrative was on the absorption of iron oxide. The Petitioner cited several publications and safety evaluations that addressed absorption of iron oxide, focusing primarily on the Joint FAO/WHO Expert Committee on Food Additives (JECFA) safety review (JECFA, 1983). In particular they referenced the publication (Derman *et al*., 1977) that the JECFA used in making their determination that iron oxides and hydrated iron oxides were poorly bioavailable in humans (Table 3.), as well as rodent and avian studies by Doty *et al* (1975) and Fritz *et al* (1970). (**Reviewer's note**: The JECFA also referred to a publication by Hofvander (1968) that evaluated the occurrence of siderosis in Ethiopians as further support for their decision on the low bioavailability of iron oxide in humans. In that study, the author noted that cereal grain from that region contained high levels of iron absorbed from the iron-rich soil. Based on the study data, he estimated that consumption of these grains would result in an iron intake of approximately 500 mg/day in that population. However, this level of exposure was not reported to result in siderosis, primarily due to iron contamination being in the form of iron oxide and hydroxides.) In addition, a few studies on experimental animals (dogs and cats) indicated that relatively high levels of iron oxide in the diet (up to 10 g/kg) did not result in adverse effects. The Petitioner also noted that rats consuming more than 50 mg/kg of body weight of iron oxide for 8 generations showed no effects on reproduction. Based on the low bioavailability of these compounds, JECFA established an ADI of 0.5 mg/kg bw for the iron oxides and iron hydroxides (JECFA, 198). (**Reviewer's note:** The above mentioned studies in dogs and cats and the eight generation rat study were submitted to the FDA as support for the safety of the use of iron oxides in cat and dog foods (CAP 51, 21 CFR 73.200), and are incorporated by reference into this memorandum.)

Based on the above studies, the overall bioavailability of iron oxide is considered to be <1.0%. Using this information, the Petitioner stated (page 26 of their narrative) that, "….. it is reasonable to conclude that an assumption that 1% of iron from ingested iron oxide will be absorbed in humans is a conservatively high level."

Table 3.

Reference	Material	Methods	Results
Derman *et al*. 1977	ferric oxide	12 Indian women	0.01% absorption of iron from iron oxide from porridge with no ascorbic acid, 0.5% absorption with ascorbic acid
Doty *et al*. 1975 (as cited in SCOGS 1980)	ferric oxide	rats (via gavage)	0.7% iron absorbed (99.3% recovered in feces)
Fritz et al. 1970	ferric oxide	anemic rats and chicks	0-6% iron absorption relative to iron from iron sulfate
Hofvander, 1968		Analysis of uptake of iron in Ethiopians from consumption of cereal grains grown in iron-rich soil	No siderosis observed in any of the population, leading to the conclusion that the absorbed iron was in the form of iron oxide or hydroxide.

Petitioner's review of the preclinical safety of iron oxide

The Petitioner conducted a systematic search of the literature in PubMed/MEDLINE using the following search terms: ferric oxide yellow, C.I. Pigment Yellow 42, iron (III) oxide monohydrate, iron oxide monohydrate yellow, iron oxide yellow, or CAS No. 51274-00-1; iron (III) oxide, iron oxide red, ferric oxide, ferric oxide red, ferrous-ferric oxide, iron oxides, CAS No. 1309-37-1; ferrosoferric oxide, iron oxide (Fe_3O_4), black powder, CAS No. 1317-61-9. The search limits, "safe, toxicology, toxic, toxicity, hazard, risk, health, in vitro, human, animal" were applied and all relevant articles in English or with English abstracts were also captured.

Acute toxicity

The Petitioner cited the 1980 Select Committee on GRAS Substances (SCOGS) report on the acute oral toxicity (LD50) for iron oxide for rats and mice of >15 g/kg. They also cited information from the International Uniform Chemical Information Database (IUCLID) (data reports from the European Chemicals Industry) (IUCID 2000a Fe_2O_3, page 40, and 2000b Fe_3O_4, page 17) on oral LD50s for iron oxide red (Fe_2O_3) and iron oxide black (Fe_3O_4) of >10 g/kg in the rat. It should be noted that, with the exception of the study referred to in

the SCOGS report, the acute toxicity studies cited by the Petitioner were apparently conducted by companies within the EU chemical industry and were not published in the peer-reviewed literature.

Short-term toxicity

The Petitioner referred to a Bayer AG Leverkusen study (IUCLID 2000a, page 46) in which male BDV BDIX rats were fed iron oxide red for 21 days at doses of 0, 700, 1160, 1610 or 2060 mg/kg diet. In this study there was no observed increase of liver non-hemoglobin iron content in any of the animals, at any dose.

Long-term/Chronic toxicity

The Petitioner cited the 1980 SCOGS report as a reference for a study in which dogs (N=10) were fed diets containing iron oxide colorant (570 mg/lb diet) for one to nine years. Daily consumption was estimated to be 428 mg/dog. Two of the dogs had loose stools, otherwise there were no adverse effects reported. (**Note:** This reviewer was unable to find mention of this particular study in the referenced SCOGS report. However, the JECFA did reference it in their 1983 report. The study was cited as coming from the Carnation Company in 1963, with no other reference. See additional note under section on iron oxide absorption.)

Genotoxicity Testing

The Petitioner referenced the 1997 Chemical Carcinogenesis Research Information System summaries of four Ames tests that were conducted by Fujita *et. al.* (Fujita, *et al.,* 1994) using *S. typhimurium* strains TA97 and TA102 that showed that Iron (III) oxide red was negative for this assay, with or without S9 activation. They also referenced industrial studies (IUCLID, 2000a) that showed that iron oxide red was negative in the Ames tests for *S. typhimurium* strains TA94, TA98, and TA100, with and without S9. Iron oxide red was also found to be negative in a chromosome aberration assay at concentrations of 0.0313 – 0.125 mg/ml without metabolic activation (IUCLID 2000a). Similarly, iron oxide black was found to be negative in the Ames assay with *S. typhimurium* TA 1535, TA1537, TA 1538, TA100, TA98 and TA90, with and without metabolic activation (IUCLID 2000b).

Reproductive and Developmental Toxicity

The Petitioner referenced an eight-generation Wistar rat study conducted by the Carnation Company (1963) that was cited in the 1983 JECFA report. In this study, dog food containing 570 mg of iron/lb as iron oxide was fed continuously to rats that ate an estimated 25 mg of iron/day, assuming 20 g/day of dog food consumption. No signs of toxicity were evident and no adverse effects were noted in reproductive performance. The JECFA primarily used this study, along with reviews conducted in 1974, 1978 and 1979, as the basis for their iron oxide and hydrated iron oxide Acceptable Daily Intake (ADI) of 0.0 - 0.5 mg/kg bw/day.[2] (**Reviewer's note:** No toxicological monograph was published that detailed this decision.)

Human Toxicity

The Petitioner conducted an extensive systematic review (detailed on pages 35 and 36 of the Petitioner's narrative) in assessing the adverse effects of dietary and medicinal iron overload on the various bodily systems and in subpopulations with abnormal iron handling capabilities. The review focused primarily on heme and non-heme (soluble) iron rather than on the iron oxides, and constituted a discussion of highly bioavailable forms of iron and their potential to affect human nutrition and disease, and to produce toxicity and/or cancer.

One of the major points of their review addressed an autosomal, recessive disorder known as hereditary hemochromatosis, which affects 1 in 200 and 1 in 400 individuals of northern European ancestry. This disorder is characterized by excessive absorption of food iron associated with the failure to store the additional iron in reticuloendothelial cells. The iron intake in this subpopulation is in the normal range, with the main symptoms related to improper iron storage. Because of their low level of solubility and low potential for absorption (<1.0%), consumption of iron oxides is unlikely to be a significant issue for those patients with this condition.

They also evaluated the effect of consumption of high levels of elemental iron on the gastrointestinal (GI) tract. They noted that high-dose iron supplements (primarily when taken on an empty stomach) are commonly associated with constipation and other effects, such as nausea, vomiting and diarrhea. The severity of iron toxicity is related to the amount of elemental iron absorbed. Symptoms occur with doses between 20 and 60 mg/kg with the low end of the range associated primarily with gastrointestinal irritation while systemic toxicity occurs at the high end (McGuigan, 1996; Chang and Rangan, 2011). (**Reviewer's note:** The IOM referenced these two studies in their review for establishing a Dietary Reference Intake for iron; however, they noted that the results from acute studies are not used in

[2] It should be noted that this study was supplied to the JECFA by the US FDA. The study was originally submitted in support of the use of iron oxides in cat and dog food (CAP 51, 1968).

establishing ULs for vitamins and minerals. Page 357 of *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*). Because iron oxides have relatively low solubility, it is unlikely that they would significantly contribute to the gastric irritation attributed to consumption of high levels of heme and non-heme iron.

Other sections of the Petitioner's clinical review addressed systemic changes related to the absorption of heme and non-heme iron, as well as total iron status. The following is a brief summary of the Petitioner's findings;

- There was no association between total or non-heme intake and **coronary heart disease** (CHD); however, there was a positive association between heme iron intake and CHD, especially in males.
- There was no association between total or non-heme iron intake and **breast cancer** and an inconsistent association between heme iron intake and **breast cancer**; there was a negative (protective) association between total iron intake and **colon cancer** and an inconsistent association between heme iron intake and **colon cancer**; there was no association between any form of iron intake and **endometrial cancer**; there was an inconsistent association between heme iron intake and **lung cancer**
- There is no association between total and non-heme iron intake and **diabetes**, and a consistent positive association between heme iron intake and **diabetes**
- The current evidence for an association between iron status or iron intake and **neurodegenerative diseases**, such has Alzheimer's or Parkinson's, is too sparse to draw conclusions

The following table (Table 4), along with Table 3 assessing the absorption of iron oxides, summarizes the publications that the Petitioner included in their petition that were pertinent to the toxicity of iron oxides.

Table 4.

Reference	Material	Methods	Results
Chemical Carcinogenesis Research Information System. Iron (III) Oxide. National Library of Medicine, NIH. 1997.	Ames test summary (four studies conducted in 1994 by Fujita et. al.)	*S. tryphimurium* TA97 and TA102, with and without S9 activation	Iron (III) oxide red negative in all four studies
International Uniform Chemical Information Database (IUCLID). 2000.	Iron oxide red and black	Various studies using oral administration to rodents	No overt toxicity demonstrated in any of the studies.
Select Committee on GRAS Substances. 1980. Evaluation of the Health Aspects of Iron and Iron Salts as Food Ingredients	Review		

Literature Review Update:

This reviewer conducted a search of recent toxicity literature on synthetic iron oxides covering the years 2013 and 2014. The databases used for this literature search were ToxNet, PubMed and Web of Science. No additional relevant preclinical toxicology or clinical studies for any of the petitioned iron oxide compounds were identified in this search. It should be noted that there were a large number of preclinical study references that dealt with the toxicity of nanosized iron. However, the Petitioner included particle size distribution analyses for the petitioned products (HELOS Particle Size Analysis; Section L, Appendix A) showing that the iron oxide and hydroxide particle sizes were above what might be considered as the nanosize range (i.e., 1 – 100 nm).

Discussion:
According to the study results cited by the Petitioner, the overall safety of the iron oxides is quite high. This safety appears to be primarily attributable to the low GI solubility of these compounds that results in a low iron uptake (<1%) by the small intestine and, therefore, reduced potential for these compounds to produce systemic toxicity. This low bioavailability forms the gist of the Petitioner's argument on the safety of iron oxides for their petitioned uses. Although the animal and human data they relied on to make this argument is somewhat sparse and some of it dated, there have been no subsequent studies that contradict this finding.

In assessing human exposure to iron from the petitioned products, DPR's chemists estimated CEDIs for total iron from iron oxides at the 90th percentile in all populations as being below the ULs established for total iron (heme and non-heme iron) by the IOM (Table 1). The exposure estimates for bioavailable iron from iron oxides (using 1% bioavailability) were also well below the IOM UL at the 90th percentile.

Conclusion: Given the low level of toxicity and low dietary exposure (bioavailability) of synthetic iron oxides (red, yellow, black), DPR Toxicology concludes there is a reasonable certainty of no harm from the use of synthetic iron oxides as colorants in sugar-sweetened and sugar-free hard and soft candies, pressed mints and chewing gum.

References:

Carnation Co. (1967) Rat multi-generation reproduction study. Rat iron retention study (unpublished studies). Submitted to WHO JECFA by the United States Food and Drug Administration.

Chang TP, Rangan C. 2011. Iron poisoning: a literature-based review of epidemiology, diagnosis, and management. *Pediatr Emerg Care*. 27(10):978-85.

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Fritz JC, Pla GW, Roberts T, Boehne JW, Hove EL. 1970. Biological availability in animals of iron from common dietary sources. *J Agric Food Chem*. 18(4):647-51.

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Institute of Medicine (IOM). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: The National Academies Press, 2001.

International Uniform Chemical Information Database (IUCLID). 2000a. Chemical Data Sheet for Iron Oxide Red (Fe_2O_3) CAS: 1309-37-1

International Uniform Chemical Information Database (IUCLID). 2000b. Chemical Data Sheet for Iron Oxide Red ($FeO \bullet 3O4$) CAS: 1317-61-9

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1983. Toxicological Evaluation of Certain Food Additives and Food Contaminants, WHO Food Additives Series 18, Iron.

McGuigan MA. 1996. Acute iron poisoning. Pediatr Ann. 25:33–38.

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