世卫组织对食品添加剂亚铁氰化物的毒理学评价

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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

WORLD HEALTH ORGANIZATION

TOXICOLOGICAL EVALUATION OF SOME FOOD COLOURS, ENZYMES, FLAVOUR ENHANCERS, THICKENING AGENTS, AND CERTAIN FOOD ADDITIVES

WHO FOOD ADDITIVES SERIES 6

The evaluations contained in this publication were prepared by the Joint FAO/WHO Expert Committee on Food Additives which met in Rome, 4-13 June 1974[1]

World Health Organization Geneva 1975

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[1] Eighteenth Report of the Joint FAO/WHO Expert Committee on Food Additives, Wld Hlth Org. techn. Rep. Ser., 1974, No. 557. FAO Nutrition Meetings Report Series, 1974, No. 54.

世界卫生组织

对若干食用色素、酶、增味剂、增稠剂等食品添加剂的毒理学评价

世界卫生组织 食品添加剂系列 6

本出版物所载的评价是由粮农组织/世界卫生组织食品添加剂联合委员会（JECFA）于 1974 年 6 月 4 日至 13 日在罗马举行的会议编写[1]

世界卫生组织，日内瓦，1975 年

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[1] 粮农组织/世界卫生组织 食品添加剂联合专家委员会 第十八次报告，世界卫生组织 技术报告集，1974 年第 557 号。粮农组织营养会议报告系列，1974 年第 54 号。

亚铁氰化钙、亚铁氰化钾和亚铁氰化钠说明

CALCIUM, POTASSIUM AND SODIUM FERROCYANIDE

Explanation

These compounds have been evaluated for acceptable daily intake by the Joint FAO/WHO Expert Committee on Food Additives (see Annex 1, Refs Nos 20 and 34) in 1969 and 1973.

Since the previous evaluation additional data have become available and are summarized and discussed in the following monograph. The previously published monographs have been expanded and are reproduced in their entirety below.

BIOLOGICAL DATA

BIOCHEMICAL ASPECTS

Because of the strong chemical bond between iron and the cyanide groups these salts have a low toxicity. Dogs injected i.v. with sodium ferrocyanide (0.5 gm/kg bw), excreted the salt without renal damage demonstrated by high urea clearance, absence of gross or microscopic haematuria. Repeat clearance several weeks after injection was found to be entirely normal without chronic haematuria, albuminuria or cylindruria. Sodium ferrocyanide, inulin and creatinine show the same excretory behaviour in respect to plasma clearance. In the dog ferrocyanide is probably excreted entirely by glomerular filtration (Van Slyke et al., 1935; Berliner et al., 1950; and Chinard, 1955). I.v. infusion of ferrocyanide and creatinine (20 mg/litre) only dogs gave an average clearance ratio of 0.966 ± 0.41. Ferrocyanide clearance ratios showed no relationship to plasma ferrocyanide concentration (Berliner et al., 1950). "Instantaneous" injection into renal artery of dogs of combinations of inulin, creatinine and sodium ferrocyanide showed that there was no displacement of one glomerular substance with respect to another in spite of very rapid changes in serum concentration (Chinard, 1955).

Rabbits injected i.v. with either sodium or calcium ferrocyanide (0.25 gm/kg bw), showed similar rates of excretion of ferrocyanide in the urine. In another experiment rabbits were injected i.v. with either sodium, calcium or magnesium ferrocyanide and histochemical studies made on the kidneys to determine ferrocyanide distribution. Ferrocyanide appeared to be eliminated via the glomeruli. There was no evidence of tubular excretion. Some storage of ferrocyanide occurred in the proximal convoluted tubule cells after the urine was free of demonstrable ferrocyanide (Gersch & Stieglitz, 1934).

1969 年和 1973 年，FAO/WHO Expert 食品添加剂联合委员会（见附件 1，参考文献第 20 号和第 34 号）对这些化合物的可接受每日摄入量进行了评估。

自上次评估以来，已经有了额外的数据，并在以下专著中进行了总结和讨论。以前出版的专著已经扩展并完整复制如下。

生物数据

生化方面

由于铁和氰化物基团之间的强化学键，这些亚铁氰化物具有低毒性。狗静脉注射亚铁氰化钠（0.5 gm/kg bw），排泄盐而无肾损伤，表现为尿素清除率高，无肉眼或镜下血尿。注射后数周重复清除发现完全正常，无慢性血尿、白蛋白尿或柱状尿。亚铁氰化钠、菊粉和肌酐在血浆清除方面表现出相同的排泄行为。在狗中，亚铁氰化物可能完全通过肾小球过滤排泄（Van Slyke et al，1935： Berliner et al，1950；and Chinard，1955）。仅静脉注射亚铁氰化物和肌酐（20mg/L）的狗的平均清除率为 0.966±0.41。亚铁氰化物清除率与血浆亚铁氰化物浓度无关（Berliner 等人，1950），将菊粉、肌酐和亚铁氰化钠的组合“瞬间”注射到狗的肾动脉中，结果表明，尽管血清浓度变化非常迅速，但一种肾小球物质并未被另一种肾小球物质取代（Chinard，1955）。

静脉注射亚铁氰化钠或亚铁氰化钙（0.25 gm/kg bw）的兔子，尿液中亚铁氰化物的排泄率相似。在另一项实验中，向兔子静脉注射亚铁氰化钠、钙或镁，并对肾脏进行组织化学研究以确定亚铁氰化物分布。亚铁氰化物似乎通过肾小球消除。没有肾小管排泄的证据。在尿液排泄后，近端卷曲小管细胞中可检测到亚铁氰化物（Gersch & Stieitz,1934）

Following i.v. injections of sodium ferrocyanide in amounts ranging from 0.55-6.2 gm into humans ferrocyanide and urea clearance rates were found to be essentially similar suggesting that ferrocyanide was excreted like urea with about 40% reabsorption. Subjects receiving excessive doses of ferrocyanide (5X recommended) developed a marked albuminuria accompanied by numerous granular casts, white cells, epithetical cells and rare red blood cells. Symptoms disappeared within two weeks. There was no change in urea clearance during this period (Miller & Winkler, 1936). 0.1% sodium ferrocyanide was administered by i.v. infusion to six infants, nine days to 14 months of age. The comparative rate of glomerular filtration of inulin and sodium ferrocyanide suggested tubular reabsorption of the latter substance in infants. There was no evidence of urinary disturbance in infants given sodium ferrocyanide (Calcagno et al., 1951).

Female dogs 10-20 kg were injected (i.v.) with 1000 mg of ferrocyanide. 94-98% of the administered ferrocyanide was recovered in the urine in 24 hours. Ferrocyanide could not be detected in red blood cells, gastric juice or faeces (Kleeman et al., 1955).

Rats dosed orally with 200 mg/kg potassium ferrocyanide excreted about 47% unchanged in the faeces and 3% in the urine. Faecal and urinary excretion of ferrocyanide and thiocyanate was at a maximum from days 1 to 3 after dosing, and thereafter declined to a low level (Gage, 1950).

A group of nine human subjects, which included patients with liver and kidney damage were injected (i.v.) with 30-50 mg of Fe^{59-} labelled ferrocyanide. In the normal subject an average of 80% (68-87%) of the administered radioactivity was recovered in 24-48 hours. There was no significant radioactivity detected in pooled faeces, saliva or gastric juice. In normal subjects the half time value (T 1/2) was 135 minutes. The rate of disappearance was slower in patients with renal damage. There was some evidence of <u>in vivo</u> binding of ferrocyanide to plasma albumin. In dogs the T 1/2 of labelled ferrocyanide was 40-50 minutes. No significant radioactivity was found in the pooled faeces, saliva or gastric juices of dogs (Kleeman & Epstein, 1956).

Glomerular function was studied in 115 humans, 45 healthy, 70 patients with glomerulonephritis, hypertension and amyloidoris. 10 ml 5% sodium ferrocyanide was non-toxic in adults and 0.0077 g/kg tolerated in infants. Twenty-five per cent. was excreted in 80 minutes and the remainder in the next 90 minutes by glomerular filtration. Patients had slower rates of excretion (Forero & Koch, 1942).

对人体静脉注射 0.55-6.2 gm 的亚铁氰化钠后，发现亚铁氰化物和尿素清除率基本相似，表明亚铁氰化物像尿素一样排泄，再吸收率约为40%。接受过量的亚铁氰化物剂量（推荐 5 倍）的受试者出现明显的白蛋白尿，并伴有大量颗粒管型、白细胞、表皮细胞和罕见的红细胞，症状在两周内消失，在此期间尿素清除率没有变化（Miller & Winkler，1936）。通过静脉输注对六名婴儿，年龄为 9 天至 14 个月大的婴儿进行了 0.1%的亚铁氰化钠注射。菊粉和亚铁氰化钠的肾小球滤过率的比较表明，后者在婴中肾小管再吸收。没有证据表明服用亚铁氰化钠的婴儿会出现泌尿障碍（Calcagno et al，1951）。

给 10-20 kg 的母狗注射（i.v.）1000 mg 亚铁氰化物. 94-98% 的给药亚铁氰化物在 24 小时内从尿液中回收。在红细胞、胃液或粪便中无法检测到亚铁氰化物（Kleeman et al，1955）。

大鼠口服 200 mg/kg 亚铁氰化钾，在粪便中排泄约 47%，在尿液中排泄约 3%。亚铁氰化物和硫氰酸盐的粪便和尿液排泄在给药后第 1 天至第 3 天达到最大值，此后下降到低水平 （Gage，1950）。

一组包括肝脏和肾损伤患者在内的 9 名人类受试者，被注射（静脉注射）30-50 mg 的 Fe59 标记的亚铁氰化物。在正常受试者中，平均 80%（68-87%）的施用放射性在 24-48 小时内被回收。在混合的粪便、唾液或胃液中没有检测到明显的放射性。在正常受试者中，半衰期值 （T 1/2）为 135 分钟。肾功能损害患者的消失速度较慢。有一些证据表明亚铁氰化物在体内与血浆白蛋白结合。在狗中，T 1/2 标记的亚铁氰化物为溶液会流 40-50 分钟。在狗的粪便、唾液或胃液中没有发现显著的放射性物质（Kleeman & Epstein，1956）。

对 115 例人类、45 例健康患者、70 例肾小球肾炎、高血压和任何一种尿路感染患者进行了肾小球功能研究，10 ml 5% 亚铁氰化钠成人无毒，婴儿耐受 0.0077g/kg。25%在 80 分钟内通过肾小球滤过排泄，其余部分在接下来的 90 分钟内通过肾小球滤过排出。患者的排泄速度较慢（Forero & Koch，1942）。

TOXICOLOGICAL STUDIES

Acute toxicity

Animal	Route	LD_{50} (mg/kg bw)	Reference
Rat	Oral	1 600-3 200	Fasset, 1958

Short-term studies

Rat

Groups of 10 male and 10 female rats were maintained for 13 weeks on diets containing 0, 0.05, 0.5 and 5.0% sodium ferrocyanide. Growth rate and food consumption were normal except at the 5% level, where there was slight depression. Haematocrit and haemoglobin values were depressed at the 5% level. Kidney weight of both males and females at the 5% level and females at the 0.5% level was increased as were male adrenal and female pituitary gland weights in the 5% group. The kidneys of rats at the 0.5% level showed a minimal degree of tubular damage. The effect was more marked at the 5% level, in addition granular and calcified deposits were observed (Oser, 1959).

Dog

Four groups of four male and four female beagles received in their diet 0, 10, 100 and 1000 ppm of sodium ferrocyanide for 13 weeks. No abnormalities were noted regarding appearance, behaviour, body weight change, physical condition, haematology, biochemical parameters, urinary pathology, gross and histopathology. No compound-related effects were seen (Morgaridge, 1970).

Long-term studies

No data are available.

Comments:

Human studies have demonstrated that i.v. injected ferrocyanide is excreted by glomerular filtration. Some tubular reabsorption occurs in man but not in dogs. High levels were nephrotoxic in the short-term study in rats, but studies in dogs and man showed no adverse effects. No long-term studies are available. Evaluation can be based on the animal studies and human observations.

毒理学研究

急性毒性

动物	途径	LD50	参考文献
大鼠	经口	1 600-3 200（mg/kg bw）	Fasset，1958

短期研究

大鼠

一组有 10 只雄性大鼠和 10 只雌性大鼠，在含有 0、0.05、0.5 和 5.0% 亚铁氰化钠的饲料中维持 13 周。生长速度和食物消耗量正常，但在 5% 水平上出现轻微抑制。血细胞比容和血红蛋白值降低在 5% 水平。5% 水平的雄性肾脏重量和 0.5% 水平的雌性肾脏重量增加，5% 的雄性肾上腺和雌性垂体重量也增加。0.5%水平的大鼠肾脏显示出最小程度的肾小管损伤，在 5%水平上效果更为明显。此外，还观察到颗粒状和钙化沉积物（Oser，1959 年）。

狗

四组四只雄性和四只雌性比格犬在，接受 0、10,100 和 1000 ppm 的亚铁氰化钠饲料中持续 13 周。未发现外观、行为、体重变化、身体状况、血液学、生化参数、泌尿系统病理学、身体和组织病理学方面的异常。未观察到与化合物相关的效应（Morgaridge，1970）。

长期研究

无可用数据

评估：

人类研究表明，静脉注射的亚铁氰化物通过肾小球滤过排泄。一些肾小管再吸收发生在人身上，但在狗中没有。在大鼠的短期研究中，高浓度对肾脏有毒性，但对狗和人的研究中没有显示出不良影响。没有可用的长期研究。评估可以基于动物研究和人类观察。

EVALUATION

Level causing no toxicological effect

Rat: 0.05% (= 500 ppm) in the diet equivalent to 25 mg/kg bw

Estimate of acceptable daily intake for man

0-0.025* mg/kg bw

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* Calculated as sodium ferrocyanide.

See Also:
Toxicological Abbreviations

评价

不引起毒理学效应的水平

大鼠：在饲料中 0.05%（=500 ppm）相当于 5 mg/kg 体重

评估人的每日容许摄入量（ADI）

0-0.025* mg/kg 体重

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*以亚铁氰化钠计算。另请参阅：毒理学缩写（点击-阅读）