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]

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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.

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).

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 97% 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 *in vivo* 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 amyloidosis. 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).

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 (Ozer, 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.

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