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Teratogenicity Study of Pyrroloquinoline Quinone (PQQ) Disodium Salt

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Abstract

The objective of this study was to evaluate whether Pyrroloquinoline Quinone (PQQ) disodium salt prepared by fermentation using *Methylovorus glucosotrophus* has teratogenic effects on rats when administered orally from Gestation Day 6 (GD6) to GD20 and to characterize the dose response relationship with toxicity. One hundred mated female rats were randomly assigned to 1 of 4 groups (n = 25/group). The control group received vehicle (purified water) by oral gavage once per day, and the test groups received PQQ diluted in purified water by gavage at doses of 50, 100, or 200 mg/kg bw/day daily from GD 6 to GD 20. The rats were observed daily for mortality and clinical signs. Body weight was assessed on GD 0, and every 3rd day after through GD21. Food consumption was assessed on GDs 1-2, 6-7, 9-10, 12-13, 15-16, and 19-20. On GD 21, all animals were necropsied and examined macroscopically. Ovaries and uteri were examined for litter data-those without visible implantation were placed in ammonium sulfide solution to assess whether early resorptions had occurred. Live fetuses were weighed and examined for external abnormalities. Then sex was determined and crown-rump length was measured. About half of each litter's live fetuses were fixed with modified Davidson's fixative for soft tissue examination and the remaining fetuses in were examined for skeletal examination. There were no treatment-related changes on clinical or macroscopic observations, litter data, sex ratio, fetal weights, crown-rump length, or fetal structure. No mortality was observed. Based on the results of this study, the No Observed Adverse Effect Level (NOAEL) of PQQ disodium salt was considered to be 200 mg/kg bw/day, the highest dose tested, for maternal toxicity and embryo-fetal developmental toxicity.

Keywords: *Pyrroloquinoline Quinone; PQQ Disodium Salt; Methylovorus glucosotrophus, Teratogenicity; Prenatal Development Toxicity*

Research Highlights

- PQQ disodium salt was produced via *Methylovorus glucosotrophus*.
- PQQ disodium salt did not exhibit developmental and reproductive toxicity.
- The NOAEL was 200 mg/kg bw/day, the highest level tested in rats.

Introduction

Pyrroloquinoline quinone (PQQ), also known as disodium 4,5-dihydro-4,5-dioxo-1h—pyrrolo(2,3-f) quinolone-2,7,9-tricarboxylate; methoxatin disodium salt or disodium pyrroloquinolinedione tricarboxylate, was first recognized as a novel bacterial cofactor in 1979 [1].

The primary source of PQQ in the human diet is thought to be from microbial sources, and PQQ is found in a variety of foods and in high levels in fermented soybeans, eggs, and milk [2,3]. It also has been found in the tissues and body fluids of humans and rats [2,4].

PQQ is involved in numerous physiological and biochemical processes [3]. Under appropriate conditions, PQQ is capable of catalyzing continuous redox cycling (the ability to catalyze repeated oxidation and reduction reactions), as well as oxidative deaminations [5], thus, it can serve as an antioxidant [5]. There is strong evidence PQQ may play an important role in pathways important to cell signaling. The importance of PQQ to mammalian health is evident when it is omitted from chemically defined diets. PQQ plays multiple physiological roles, such as promoting growth and reproduction, and providing neural and cardiovascular protection. It also enhances antioxidants, learning, memory, and immune function [5]. PQQ disodium salt is thought to have similar physiological and metabolic effects as PQQ [5].

The safety of PQQ manufactured by chemical synthesis or fermentation using *Hyphomicrobium denitrificans* has been demonstrated through various toxicity studies in rats, including an acute study, a 28-day repeated dose study, and multiple 90-day toxicity studies [6,7]. However, no teratogenicity study was identified in the literature although results from an unpublished teratogenicity study for PQQ disodium salt prepared by chemical synthesis [8] are partly available in the public domain. In addition, no reports are available for the PQQ disodium salt prepared via bacterial fermentation using *Methylovorus glucosotrophus*. This study is the first evaluate the teratogenic potential of PQQ disodium salt prepared by fermentation via *Methylovorus glucosotrophus*.

Materials and Methods

Materials

PQQ disodium Salt (purity, > 99.9%) was provided by Zhejiang Medicine Co., Ltd., China.

Animals

Thirty male and 120 female Crl:CD®[SD] VAF/Plus®/SPF rats (males: 319 to 396g, females: 211 - 269g; 10 weeks old) were used for mating in this study, where 100 female rats were randomly assigned to 4 study groups. One mated female was kept for possible replacement, but no replacements were required during the study. Rats were provided by BioLASCO Taiwan Co., Ltd (Taipei, Taiwan). Animals were acclimated for 6 days between receipt and mating.

Animals were supplied with rodent breeding feed from contract vendor (company name not provided) *ad libitum*. Nutritional components and environmental contaminants in the diet were analyzed routinely by the vendor and an independent laboratory, respectively. There were no known contaminants present in the diet that was expected to interfere with the test results. The analysis reports and lot numbers were on file at the Testing Facility.

Animals were provided purified water *ad libitum* by water bottles. The animal drinking water was analyzed for contaminants each quarter and water analysis reports were on file at the testing facility. No contaminants were expected to be present at levels that would interfere with the outcome of the study. The room was controlled and monitored for humidity (targeted range 40% to 70%) and temperature (targeted range 20°C to 25°C) with 10 to 20 air changes/hour. The room was on a 12-hour light/dark cycle.

In order to mate the animals, 1 or 2 virginal female rats were placed in the cage of a male. Observation of vaginal plugs or smears were taken daily each morning after pairing until a positive identification of mating occurred, which was considered Gestation Day 0 (GD0) When 101 mated animals were available, cohabitation was terminated.

Experimental procedures

Rats received 50, 100, or 200 mg/kg body weight (bw) PQQ disodium salt, or the vehicle (distilled water) daily on gestation days (GD) 6 through 20 through intragastric administration. The animals were observed at least once daily during the exposure period to record any clinical effects including mortality, moribundity, behavioral changes. The animals were weighed once daily at every 3 days during

the gestational period from GD 0 to GD21. Food consumption was assessed on GDs 1-2, 6-7, 9-10, 12-13, 15-16, and 19-20. On GD 21, all animals were necropsied and examined macroscopically. Ovaries and uteri were examined for litter data, including: number of corpora lutea per ovary, weight of gravid uterus, location and number of implantation sites, resorptions, fetal death, and number of fetuses. Those without visible implantation were placed in ammonium sulfide solution to assess whether early resorptions had occurred. Live fetuses were weighed and examined for external abnormalities. About half of each litter's live fetuses were fixed with modified Davidson's fixative for soft tissue examination and the remaining fetuses in were stained with Alizarin red solution for skeletal examination.

Guidelines and good laboratory practice (GLP)

The design of this study was based on the FDA Redbook 2000: IV.C.9.b, Guidelines for Developmental Toxicity Studies. The study was conducted in full compliance with the most recent version of the GLP regulations: 1) China Food and Drug Administration (CFDA) Good Laboratory Practice for Nonclinical Laboratory Studies, effective September 01, 2003, and 2) US FDA Good Laboratory Practice Regulations 21 CFR 58, effective June 20, 1979, as amended 52 FR 33780, Sept. 4, 1987, and subsequent amendments.

Animal welfare

All applicable portions of the study conformed to the following regulations and guidelines regarding animal care and welfare: 1) AAALAC International guidelines as reported in the Guide for the Care and Use of Laboratory Animals, National Research Council (2011), and 2) People's Republic of China, Ministry of Science and Technology, "Regulations for the Administration of Affairs Concerning Experimental Animals," 1988.

Statistical analysis

The data collected at WuXi AppTec (Suzhou) Co., Ltd. was analyzed statistically using the tests and methods described as follows. There was 1 control group (group 1) and 3 comparison groups which received 50, 100, or 200 mg/kg bw/day PQQ (Groups 2, 3, and 4; respectively). Parental in-life data, uterine, and ovarian exams was analyzed by group pair-wise comparisons. The pregnancy index malformations, variations, total malformations, and total variations by finding and exam type (litter incidence) were analyzed by Fisher's exact test. Descriptive statistics consisted of means, standard deviations, and group size for each group. Incidence (counts and percentages) was provided. Each group pairwise comparisons of interest were conducted via a two-sided test at the 5% significance level. Significant results were reported as $p \leq 0.001$, $p \leq 0.01$, or $p \leq 0.05$, where p represented the observed probability.

Whenever there were more than two groups, the homogeneity of the group variances was evaluated using the Levene's test at the 0.05 significance level. If differences between group variances were not found to be significant ($p > 0.05$), then a parametric one way analysis of variance (ANOVA) was performed. When significant differences among the means were indicated by ANOVA test ($p \leq 0.05$), the Dunnett's test was used to perform the group mean comparisons between the control group and each treated group.

Results

Results of dose formulations analysis

The concentration of test article in the control formulation was lower than the Limit of Quantitation (LOQ) × DF (Dilution Factor). Concentrations of PQQ in all dose formulations at the first and last preparation met the acceptance criteria, i.e. were within 98% to 104% of nominal concentration. For each concentration, concentrations of the top, middle, and bottom portions fall within 98% to 105% of nominal values. The relative standard deviation (RSD) of top, middle, and bottom samples were within 0.09% to 1%.

Reproductive toxicity study

Mortality, fate of females, and clinical observations

No mortality was observed in the study. One female at control, 3 females at low-dose (50 mg/kg bw/d), 1 female at mid-dose (100 mg/kg bw/d), and 1 female at high-dose (200 mg/kg bw/d) mated successfully but did not result in pregnancy.

Group/parameters	Control (n = 24)	Low-dose (N = 22)	Mid-dose (N = 24)	High dose (N = 24)
No. mated females	25	25	25	25
No. non-pregnant females	1	3	1	1
No. pregnant females	24	22	24	24
No. rats with viable fetus on GD21	24	22	24	24

Table 1: *Summary of maternal fate.*

d = day.

No treatment-related clinical observations were observed in the study. The observed findings, including alopecia, coat soiled, ocular discharge, scab, and toenail missing were considered incidental due to low incidence and/or similar findings in the control animals (no data shown).

Body weights and gravid uterine weight

There were no treatment related changes on body weights (Figure 1), body weight changes as well as gravid uterine weight (data not shown), and absolute gestation weight gain (data not shown) in the study. All the above data in the treated groups were comparable to concurrent control. Figure 1 presents the mean body weights of females from GD0 to GD21, measured at the initial time point and every 3 days after.

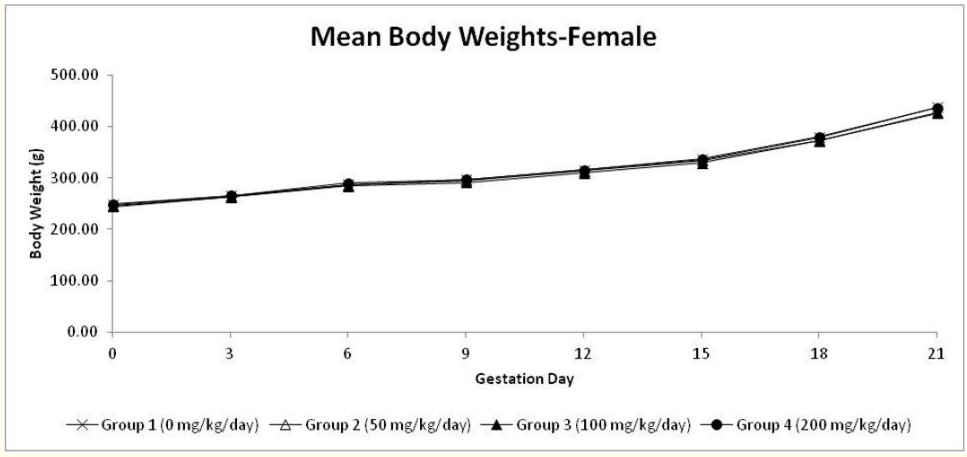

Figure 1: *Mean body weights of female rats.*

Food consumption

There were no treatment related changes on food consumptions in the study (data not shown). The food consumptions in treated groups were comparable to control group.

Litter data, sex ratio, fetal crown-rump length, and fetal weight

There were no significant differences between any PQQ dose groups and the control group for the mean number of corpora lutea, implantation sites, live fetuses, pre- and post-implantation loss, fetal crown-rump length and sex ratio in the study. All these data in the treated groups were comparable to concurrent control group (Table 2 and 3).

Parameters	Control	Low-dose	Mid-dose	High dose
Viable Fetuses	15.8 (2.7)	14.2 (3.2)	14.2 (3.2)	14.6 (2.9)
% males	52.3 (14.9)	51.3 (14.2)	51.3 (14.2)	50.5 (14.2)
Dead Fetuses	0.04 (0.20)	0 (0)	0 (0)	0.04 (0.20)
Embryonic resorptions	0.08 (0.28)	0.18 (0.50)	0.21 (0.66)	0.25 (0.44)
Total non-viable	0.13 (0.34)	0.18 (0.50)	0.21 (0.66)	0.29 (0.46)
Fetal weight, male (g)	5.42 (0.27)	5.72 (0.52)	5.68 (0.40)	5.68 (0.29)
Fetal weight, female (g)	5.11 (0.22)	5.43 (0.48) *	5.37 (0.30)	5.40 (0.28) *
Fetal C-R length, male (mm)	43.23 (1.34)	43.99 (1.75)	43.85 (1.23)	44.04 (0.91)
Fetal C-R length (female) (mm)	42.05 (1.18)	42.82 (1.82)	42.88 (1.35)	43.04 (0.92)

Table 2: *Summary of litter data and sex ratio*.*

**Data presented as mean (SD); *p < 0.05 compared to group 1; C-R = Crown-Rump.*

Parameters	Control	Low-dose	Mid-dose	High-dose
Corpora lutea	16.1 (2.8)	14.2 (3.6)	14.6 (3.0)	15.4 (3.3)
Implantations	15.9 (2.8)	14.0 (3.5)	14.4 (3.0)	14.9 (3.0)
Implantation loss %, pre-	0.9 (2.6)	1.4 (2.6)	1.3 (4.1)	2.7 (5.9)
Implantation loss %, post-	2.6 (1.9)	1.7 (4.8)	1.7 (4.8)	1.8 (2.9)

Table 3: *Summary of litter implantation loss*.*

**Data presented as mean (SD); The numbers in parenthesis represent percentage of implantation loss which is calculated as (number of corpora lutea - number of implantations)/number of corpora lutea × 100 post-implantation; loss (%) = (number of implantations - total number of live fetuses)/number of implantations × 100.*

Either male or female mean fetal weights increased by up to 6.3% at 3 treated groups when compared to control group, out of which female fetal weights at low-dose and high-dose reach the statistical significance. These increases in fetal weights did not relate with dose levels and no correlating significantly increased crown-rump length was observed, therefore, these were not considered treatment- related but individual variance.

Macroscopic observation of females

No gross abnormalities were observed in this study.

Developmental parameters of the F1 generations

Gross necropsy of the animals in all treatment groups in the F1 generations revealed no abnormalities in external or internal changes. There were no treatment-related abnormalities in clinical signs.

External and visceral examination of fetuses

Among 305 to 379 fetuses (22 - 24 litters) tested for each group, there were no external abnormalities including malformations and variations observed in the study (data not shown). No test article-related visceral abnormalities including malformations and variations were observed in this study (Table 4). One fetus in control group with visceral malformations such as three-chambered heart (malpositioned and misshapen) and fused lung lobes was observed. This was considered incidental. One fetus in the low-dose group was observed with visceral malformation of situs inversus in thoracic and abdominal cavity. Another fetus in the low-dose group had visceral malformation of small kidney was observed. The two findings were isolated events and not observed in the mid- or high-dose groups, and the incidence of both was within the range of historical control data [9]. Therefore, these observations were not considered treatment-related. The visceral variations including dilated renal pelvis and convoluted ureter were observed at treated groups and control. These were of the types seen in untreated rats in this laboratory and/or low incidence (the incidence was within the range of historical control data) [9].

Parameter	Control	Low-dose	Mid-dose	High dose
Fetal visceral examinations				
No. fetuses (litters) examined	184 (24)	147 (22)	162 (24)	170 (24)
No. fetuses (litters) with malformations	1 (1)	2 (2)	0 (0)	0 (0)
% fetuses (litters) with malformations	0.54 (4.17)	1.36 (9.09)	0 (0)	0 (0)
No. fetuses (litters) with variations	15 (10)	8 (7)	14 (8)	13 (11)
% fetuses (litters) with variations	8.15 (41.67)	5.44 (31.82)	8.64 (33.33)	7.65 (45.83)
Fetal visceral abnormalities				
Heart, malpositioned	1 (1)	0 (0)	0 (0)	0 (0)
Heart, misshapen	1 (1)	0 (0)	0 (0)	0 (0)
Heart, 3-chambered	1 (1)	0 (0)	0 (0)	0 (0)
General, situs inversus	0 (0)	1 (1)	0 (0)	0 (0)
Kidney (small)	0 (0)	1 (1)	0 (0)	0 (0)
Lung (fused)	1 (1)	0 (0)	0 (0)	0 (0)
Renal pelvis (dilated)	1 (1)	3 (2)	2 (1)	2 (2)
Ureter (convoluted)	14 (10)	8 (7)	14 (8)	12 (10)
Ureter (dilated)	0 (0)	1 (1)	2 (1)	0 (0)

Table 4: *Summary of fetal visceral examinations of F1 newborn pups in the reproductive toxicity study. Data presented as mean(SD)*

Skeletal examination of fetuses

As shown in table 5, no test article-related skeletal abnormalities including malformations and variations were observed in this study. The skeletal variations, including incomplete ossification of hyoid, bipartite ossification of lumbar centrum, nodulated rib, short supernumerary rib, short rib, incomplete ossification of sternebra, unossified sternebra, bipartite ossification of thoracic centrum, and dumbbell-

shaped thoracic centrum, were observed at treated groups and/or control. These findings were of the types seen in untreated rats in this laboratory and/or low incidence [9].

Parameter	Control	Low-dose	Mid-dose	High dose
Fetal skeletal examinations				
No. fetuses (litters) examined	195 (24)	156 (22)	178 (24)	181 (24)
No. fetuses (litters) with malformations	0 (0)	0 (0)	0 (0)	0 (0)
% fetuses (litters) with malformations	0 (0)	0 (0)	0 (0)	0 (0)
No. fetuses (litters) with variations	26 (16)	19 (11)	13 (7)	13 (9)
% fetuses (litters) with variations	13.33% (66.67%)	12.18% (50.00%)	7.30% (29.17%)	7.18% (37.50%)
Fetal skeletal abnormalities				
Hyoid, incomplete ossification	11 (9)	2 (2*)	4 (4)	0 (0**)
Lumbar centrum, bipartite ossification	1 (1)	0 (0)	0 (0)	0 (0)
Rib, nodulated	1 (1)	0 (0)	1 (1)	0 (0)
Rib, short	0 (0)	0 (0)	1 (1)	1 (1)
Rib, supernumerary, short	11 (8)	16 (9)	6 (3)	9 (6)
Sternebra, incomplete ossification	1 (1)	0 (0)	0 (0)	1 (1)
Sernebra, unossified	0 (0)	0 (0)	1 (1)	0 (0)
Thoracic centrum, bipartite ossification	0 (0)	0 (0)	0 (0)	2 (2)
Thoracic centrum, dumbbell-shaped	1 (1)	1 (1)	0 (0)	0 (0)

Table 5: *Summary of fetal skeletal examinations of F1 newborn pups in the reproductive toxicity study.*
**p < 0.05 vs. control, Fisher's Exact Test; **p < 0.01 vs. control, Fisher's Exact Test. Data presented as mean(SD)*

Discussion

In the present study, mated females were orally treated with PQQ disodium salt at daily dose levels of 0, 50, 100, and 200 mg/kg bw from GD 6 to 20. This study demonstrated that PQQ at daily doses up to 200 mg/kg bw did not exhibit teratogenic effects in pregnant rats. No adverse effects including body weight gains or animal death were observed. No treatment-related abnormalities were noted in fetal embryo development such as appearance, visceral, and skeletal malformations. Relative to the vehicle control, there was also no effect of PQQ treatment on pregnancy rates, implantation, pregnancy length, gender ratios, viability indexes, lactation indexes, prenatal death rates, the number of live young at time of birth, organ weights and indexes and necropsy or histopathological examination parameters. Thus, the NOAEL was set at 200 mg/kg for parent animals and their offspring.

A teratogenicity study of another source of PQQ disodium salt reported similar results. The China Center for Disease Control and Prevention (CDC) conducted an unpublished teratogenicity study for PQQ disodium salt at doses up to 1,250 mg/kg bw/day on 96 pregnant Wistar rats for 20 gestational days [8]. PQQ disodium salt had no significant effects on embryo survival and development, fetal gross malformations, and fetal bone and organ development. There were declines in body weight on days 9 and 12 in the highest does group, but they were transient and therefore not considered related to treatment. They concluded there were no teratogenic effects at any dose tested up to 1,250 mg/kg bw/day.

A study in mice indicated there was no treatment-related sperm abnormalities at any dose level (up to 1,840 mg/kg bw/day) of PQQ disodium salt prepared by chemical synthesis (GRN 625, page 37) [9]. Steinberg., *et al*. [10] performed an 8 week reproductive efficacy

study in Balb/c mice at a dose of 6 μM/g PQQ/kg of diet (or ~0.3 mg/kg bw/day). Measurements included successful mating, conception, fertility, pup viability, and pup growth. The study reported no adverse effects on any parameters, reproductive or otherwise-conversely, the absence of PQQ reduced reproductive performance. Steingberg., *et al*. [11] had previously performed another reproductive performance study where female BALB/c mice were fed 500 μg/kg bw/day PQQ prior to mating, during gestation, and during lactation. Upon weaning, pups were fed the same diets for 20 weeks. No adverse effects were noted on reproduction, growth, or lymphoid organ weights. Zhang., *et al*. [12] examined reproductive efficacy of PQQ disodium salt in Sprague-Dawley rats at concentrations of 0, 0.2, 0.4, 0.8, or 1.6 mg/kg bw/day from GD1 to postnatal day (PD) 21. Measurements included number of implanted embryos per litter, number of viable fetuses per litter, weight of uterine horns with fetuses, and mRNA expression of CAT, GPx2, SOD1, S1c2a1, and S1c2a3 in the placenta. This study also reported no adverse effects on any parameters, and benefits to reproductive performance with PQQ.

Our study found the NOAEL for maternal and developmental toxicity of PQQ disodium salt as 200 mg/kg bw/day, the highest level tested for this teratogenicity study. The NOAEL determined in this study is in consistent with those reported from another toxicity studies including a teratogenicity study [8] and a 90 day toxicity study [6].

Conclusion

From the teratogenicity study of PQQ disodium salt produced via fermentation with *Methylovorus glucosotrophus* in rats, the NOAELs for both maternal and developmental toxicity were set at 200 mg/kg bw/day, the highest level tested.

Acknowledgments

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Conflict of Interest

The authors report that Wan Zhang is employed by Zhejiang Medicine Co., Ltd., the sponsor of the study. However, the authors declare that her employment status may not be considered as potential competing interests.

Author Contributions

Albert W. Lee and Iris L. Case analyzed and interpreted the data and drafted and finalized the manuscript. Zhijia Ding, Dong Shao, Xiaoping Zhang, Jing Chen organized the study plan, prepared the test substance and analyzed and interpreted the data. Wan Zhang, the corresponding author, secured the fund to sponsor this study, organized the study plan, oversaw the entire study, and decided to publish the data.

Bibliography

1. Salisbury SA., *et al*. "A novel coenzyme from bacterial primary alcohol dehydrogenases". *Nature* 280.5725 (1979): 843-844.
2. Kumazawa T., *et al*. "Levels of pyrroloquinoline quinone in various foods". *Biochemical Journal* 307.2 (1992): 331-333.
3. Misra HS., *et al*. "Pyrroloquinoline-quinone and its versatile roles in biological processes". *Journal of Biosciences* 37.2 (2012): 313-325.
4. Noji N., *et al*. "Simple and sensitive method for pyrroloquinoline quinone (PQQ) analysis in various foods using liquid chromatography/electrospray-ionization tandem mass spectrometry". *Journal of Agricultural and Food Chemistry* 55.18 (2007): 7258-7263.
5. Rucker R., *et al*. "Potential physiological importance of pyrroloquinoline quinone". *Alternative Medicine Review* 14.3 (2009): 268-277.

6. Liang C., *et al*. "A subchronic oral toxicity study on pyrroloquinoline quinine (PQQ) disodium salt in rats". *Food and Chemical Toxicology* 75 (2015): 146-150.

7. Nakano M., *et al*. "Acute and subchronic toxicity studies of pyrroloquinoline quinone (PQQ) disodium salt (BioPQQ™) in rats". *Regulatory Toxicology and Pharmacology* 70.1 (2014): 107-121.

8. China Center for Disease Control and Prevention, National Center for Food Safety Risk Assessment. PQQ Toxicology Test Report #2. Unpublished study cited in US FDA 2016 (GRN 625) (2012).

9. US FDA. GRN 625 (2016).

10. Steinberg F., *et al*. "Pyrroloquinoline quinone improves growth and reproductive performance in mice fed chemically defined diets". *Experimental Biology and Medicine* 228.2 (2003): 160-166.

11. Steinberg FM., *et al*. "Dietary pyrroloquinoline quinone: growth and immune response in BALB/c mice". *Journal of Nutrition* 124.5 (1994): 744-753.

12. Zhang B., *et al*. "Effect of pyrroloquinoline quinone disodium in female rats during gestating and lactating on reproductive performance and the intestinal barrier functions in the progeny". *British Journal of Nutrition* 121.7 (2019): 818-830.

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