Safety Assessment of Inositol as Used in Cosmetics

Status:	Scientific Literature Review for Public Comment
Release Date:	March 28, 2024
Earliest Possible Review:	June 3 – 4, 2024

All interested persons are provided 60 days from the above release date (i.e., until May 26, 2024) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651
cirinfo@cir-safety.org

ABBREVIATIONS

ADME	absorption, distribution, metabolism, and excretion
BMI	body mass index
C_{max}	maximum observed plasma concentration
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
CLP	classification, labeling, and packaging
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI)
ECHA	European Chemicals Agency
ED_5	median effective dose
EFSA	European Food Safety Authority
EU	European Union
FDA	Food and Drug Administration
HESS	Hazard Evaluation Support System
HET-CAM	hen's egg test chorioallantoic membrane
HRIPT	human repeated insult patch test
LD_{50}	median lethal dose
log K_{ow}	n-octanol/water partition coefficient
MMP	mitochondrial membrane potential
NR	none reported
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PKB	protein kinase B
QSAR	quantitative structure-activity relationship
TG	test guideline
T_{max}	time to peak concentration
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This assessment reviews the safety of Inositol as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*; wINCI), Inositol is reported to function in cosmetics as a hair-conditioning agent and humectant.[1]

Inositol is present in foods, and commonly consumed as a dietary supplement,[2] and Inositol is generally recognized as safe (GRAS) in the US for use in foods and infant formula [21CFR184.1370, 21CFR582.5370]. Daily exposure from food use would result in much larger systemic exposure than those from cosmetic products; therefore, the primary focus of this safety assessment on Inositol as used in cosmetics is the potential for local effects from topical exposure.

It should be noted that studies were found in the literature evaluating the metabolism of Inositol administered via methods that would result in high amounts of systemic exposure (i.e., intravenous and intraperitoneal administration). These studies were not included in the report as the systemic exposure via topical administration of Inositol is expected to be much lower than these methods of administration. In addition, studies were found in the literature regarding the use of Inositol as an oral supplement for various diseases. While summaries regarding the efficacy of Inositol for the treatment of these diseases are not provided in this report, a brief summary of the adverse effects observed in these studies can be found in the Clinical Studies section of this report.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted March 2024. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

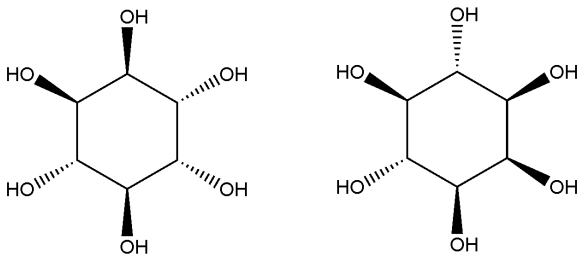
Inositol has 9 potential geometric isomers (see Chemistry section for further details). According to the *Dictionary*, the two isomers used in the production of cosmetic ingredients are *myo*-inositol and D-*chiro*-inositol.[3] Therefore, data on the remaining 7 isomers have not been provided in this report, as they are unlikely to be used in cosmetics. In addition, when the isomer of Inositol used in studies presented throughout the report is known, the isomer-specific name will be identified (e.g., Inositol (as *myo*-inositol)), as appropriate. When the specific isomer is unknown, the terms "inositols" or "an inositol" will be used throughout report text, in lower-case letters, along with the notation "isomer unspecified," in parenthesis.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[4] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

Inositol (CAS No. 87-89-8; 643-12-9) is a cyclohexyl polyol containing 6 hydroxyl functional groups, 1 per cyclohexyl carbon.[5] Inositol has a structure that is similar to the cyclic form of pyranose sugars, such as glucose, but does not have an oxygen atom in the ring; thus, it is considered to be a sugar alcohol.[3] Inositol has 9 potential stereoisomeric forms, 6 of which are naturally-occurring (*myo*-, D-*chiro*-, L-*chiro*-, *muco*-, *scyllo*-, and *neo*-), and 3 of which are synthetic (*allo*-, *cis*-, and *epi*-). According to the *Dictionary*, Inositol is the cyclic polyol that conforms generally to the structures below (Figure 1), inclusive only of the D-*chiro*- (CAS No. 643-12-9) and *myo*-inositol (CAS No. 87-89-8) stereoisomers:



D-*chiro*-inositol *myo*-inositol

Figure 1. Inositol

Chemical Properties

Inositol (as *myo*-inositol) is a white solid substance, with a water solubility of 28 g/100 g water (at 60 °C).[4] D-*chiro*-Inositol has a molecular weight of 180.16 g/mol[6] and log K_{ow} = 2.60,[4] and *myo*-inositol has a molecular weight of 180.16 g/mol and log K_{ow} = -2.08.[7] Other chemical properties of Inositol (both *myo*-inositol and D-*chiro*-inositol) be found in Table 1.[4,6-9]

Method of Manufacture

The following methods of manufacturing are general to the production of the Inositol (both *myo*-inositol and D-*chiro*-inositol), and it is unknown whether these methods are used in the manufacture of Inositol for use in cosmetics.

Inositol *(*as *myo*-inositol) has been reported to be produced via hydrolysis, microbial fermentation, and in vitro enzymatic biocatalysis.[10] In conventional chemical acid hydrolysis, phytate is abstracted and purified via soaking, neutralization, and filtration. Phytate is hydrolyzed to produce *myo*-inositol via the use of inorganic acid under high temperature and pressure. Crude *myo*-inositol is concentrated and crystallized to produce refined *myo*-inositol. Modern hydrolysis production of *myo*-inositol includes the heating of a 40% aqueous solution of phytate with a catalyst consisting of glycerin, urea, and calcium carbonate. After a cooling period, the hydrolysate is cooled, filtered, crystallized, and washed to obtain refined *myo*-inositol.

For microbial fermentation, Inositol (as *myo*-inositol) is biosynthesized via the synergetic utilization of glucose and glycerol in *Escherichia coli*. In vitro cascade enzymatic biocatalysis involves the transformation of various substances (e.g., maltodextrin, amylose, starch, cellodextrins, sucrose, xylose) to *myo*-inositol with the use of several enzymes (e.g., maltodextrin phosphorylase, phosphoglucomutase, inositol 1-phosphate synthase).

Inositol stereoiosomers (such as D-*chiro*-inositol) can be prepared from *myo*-inositol by didehydroxylation.[11] D-*chiro*-Inositol may also be synthesized from a chiral chloro-diol produced by dihydroxylation of chlorobenzene in the presence of *Pseudomonas putida* strain 39/D.[12] According to 21CFR184.1370, inositols, or *myo*-inositol, occurs naturally, and is prepared from an aqueous (0.2% sulfur dioxide) extract of corn kernels by precipitation and hydrolysis of crude phytate.

Impurities

No impurities data are available for Inositol as a cosmetic ingredient; however, purity information on Inositol (as *myo*-inositol) as a feed additive for fish, dogs, and cats has been provided by the European Food Safety Authority (EFSA).[8] Samples of Inositol (as *myo*-inositol) used as a feed additive were reported to have purities ranging from 99.3 - 99.9%. In addition, samples were reported to contain < 0.3% D-mannitol, < 0.3% propane-1,2,3-triol, < 0.5 mg/kg lead, < 0.1 mg/kg arsenic, < 0.01 mg/kg cadmium, < 0.01 mg/kg mercury, and < 0.128 ng dioxins and dioxin-like polychlorinated biphenyls. According to the Food Chemicals Codex specifications, Inositol (as *myo*-inositol) must have a purity of ≥ 97%.[13]

Natural Occurrence

Inositol is an ubiquitous substance found in living organisms, that may be present as a free sugar alcohol or as a headgroup of membrane lipids.[14] Inositol plays an important role in several biological functions such as maintaining metabolic homeostasis and cytoskeleton remodeling.[15-17] Of the 9 possible stereoisomers, *myo*-inositol is the predominant form of inositol found in the human body; however D-*chiro*-inositol may also be found.[18] In addition, *myo*-inositol can be converted in the body to D-*chiro*-inositol via a nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate-dependent epimerase enzyme.[19] In mammals, inositols are produced in the liver and kidneys at a rate of approximately 4 g/d.[3]

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics and does not cover its use in airbrush delivery systems. Data included herein were obtained from the FDA's Voluntary Cosmetic Registration Program (VCRP) database in 2023 (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) in 2022 (maximum use concentrations). The data were provided by cosmetic product categories, based at that time on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 did not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 VCRP survey data, Inositol is used in 212 total formulations (185 leave-on formulations and 27 rinse-off formulations; Table 2).[20] The results of the concentration of use survey conducted by the Council indicate Inositol is used at up to 2% (in face and neck products and in moisturizing products).[21]

Ocular exposure to Inositol may occur as this ingredient is used in products used near the eye (e.g., Inositol is used in eye lotion at up to 1%). In addition, mucous membranes are exposed and incidental ingestion may occur as Inositol is reported to be used in a lipstick formulation (concentration of use not provided).

Inositol is used in a face powder formulation (concentration of use not provided), and could possibly be inhaled. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most

droplets/particles incidentally inhaled from cosmetics would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Although products containing this ingredient may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of this ingredient (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

Inositol is not restricted from use in any way under the rules governing cosmetic products in the European Union.[22]

Non-Cosmetic

Inositol is used in several industries including food, medicine, and animal feed.[23] Inositol can be found in many foods, including vegetables, nuts, fruit, milk, grains, fish, meat, and eggs.[24] The amount of Inositol (as *myo*-inositol) present in a 2500 kcal American diet is approximately 900 mg.[25] Inositol is GRAS in the US for use in foods and infant formula [21CFR184.1370, 21CFR582.5370]. Additionally, according to the U.S. FDA, inositol is used as an active ingredient in dietary supplements, prescription animal drugs, and human over-the-counter drugs.[26,27] This ingredient has been studied for use as treatment for many disorders including, but not limited to, plaque psoriasis, gestational diabetes mellitus, trichotillomania, mental health disorders, polycystic ovary syndrome, infertility, hypothyroidism, and non-alcoholic fatty liver disease.[28-72]

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Inositol (as *myo*-inositol) is actively transported by intestinal cells in a Na+- dependent manner.[73] The majority of the free Inositol is absorbed from the human gastrointestinal tract through this active transport system. Inositol is carried into cells via sodium-ion coupled transporters. The cellular uptake and absorption of Inositol may be reduced or inhibited in the presence of glucose due to the competitive affinity for the same transporter system. Glucose may also deplete Inositol levels via the activation of the glucose-sorbitol pathway. Because of this, individuals with type 2 diabetes may display altered levels of Inositol excretion compared to healthy individuals.

Details regarding the studies summarized herein can be found in Table 3. More than 98% of total ingested Inositol (as D-*chiro*-inositol) was absorbed from the gastrointestinal tract in an assay in which rats were given a diet containing 0.23% Inositol for at least 1 mo plus 1 wk.[74] Minimal amounts of the ingested Inositol were found in the feces and urine, suggesting extensive metabolism prior to excretion. The mean serum concentrations of 3 groups of rats given 2000 mg/kg Inositol (as *myo*-inositol) in distilled water were 54.4, 43.9, and 44.6 µg/ml (animals observed at different time intervals up to 24 - 48 h).[17] Supplementation of the diet of pregnant rats with 0.5% Inositol (as *myo*-inositol) resulted in increased levels of Inositol in the plasma, liver, kidneys, and intestines of offspring, and increased levels of Inositol in the milk and mammary tissues of dams.[75] A maximum plasma concentration of 0.23 mM was observed in 8-d-old rats given a formula supplemented with 114 mg/100 ml Inositol (as *myo*-inositol).[76] In a study performed in 5 female subjects given 100 mg/kg bw Inositol (as *myo*-inositol) in water (oral ingestion), the highest urinary Inositol concentration was approximately 550 µmol/mmol creatinine 275 min after test substance administration. [77] Mean maximum observed plasma concentration (C_{max}) values were similar in subjects administered oral doses of a soft gel containing 600 mg Inositol (as *myo*-inositol) and 2000 mg of Inositol (as *myo*-inositol) powder (mean C_{max} of 31.5 and 36.3 µmol/l, respectively). Similarly, in the same study, mean C_{max} values were comparable following administration of a soft gel containing 1200 mg Inositol and 4000 mg of Inositol powder (mean C_{max} of 41.5 and 45 µmol/l, respectively).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Animal

Oral

A median lethal dose (LD_{50}) of 10,000 mg/kg bw was determined for Inositol (as *myo*-inositol) in an acute oral toxicity assay performed in mice.[4] No details regarding this study were provided.

Computational

A quantitative structure activity relationship (QSAR) model (consensus model; Toxicity Estimation Software Tool v4.2.1) was used to evaluate the potential acute oral toxicity of Inositol (as *myo*-inositol) in rats.[4] The predicted acute oral LD_{50} was determined to be 19,483.68 mg/kg.

Short-Term Toxicity Studies

Animal

Oral

The effect of Inositol (as *myo*-inositol) on weight gain and the patterns of lipids in the liver was evaluated in male Wistar rats (20-d-old and 3-mo-old; number of animals per group not stated).[4] Twenty-day-old rats received 10, 100, 200, or 1000 mg/kg bw/d and 3-mo-old rats were given 5, 50, 500, or 5000 mg/kg bw/d. Controls used, but details regarding control animals not provided. All administrations occurred for 45 d via gavage (water used as vehicle). No treatment-related effects on weight gain were observed in 3-mo-old rats compared to controls. In 20-d-old rats, growth was slightly inhibited in the 1000 mg/kg bw/d group, compared to controls. No significant differences in liver lipid patterns were observed in treated animals of either age compared to controls. No other details regarding this study were provided.

Human

Oral

Ten healthy women were supplemented with 1200 mg Inositol (as D-*chiro*-inositol), once per day, for 1 mo.[78] Clinical features were evaluated at baseline and after 1 mo of supplementation. After supplementation, statistically significant ($p < 0.01$) increases in free testosterone levels and asprosin were observed. Differences between baseline and 1 mo post-treatment for all other parameters (body mass index (BMI), glycemia, insulinemia, insulin resistance, follicle-stimulating hormone, luteinizing hormone, estradiol, and dehydroepiandrosterone) measured were not statistically-significant.

Computational

No alerts for short-term oral toxicity were raised for Inositol (as *myo*-inositol) in a Hazard Evaluation Support System Integrated Platform prediction using the QSAR Toolbox v4.1 (HESS Prediction v.2.9).[4] Similarly, Inositol (as *myo*-inositol) raised no alerts for organ toxicity following short-term oral exposure when evaluated computationally (Derek Nexus 5.0.2, Nexus 2.1.1).

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Animal

Oral

The effect of Inositol (as D-*chiro*-inositol) on estrus cycles, ovary histology, serum testosterone, and ovarian aromatase was evaluated in female C57BL/6N mice (5/group).[79] Animals were given drinking water containing Inositol (5, 10, or 20 mg/d) for 21 d. A negative control group was given plain water, and a positive control group was given drinking water containing 0.5 mg/kg/d letrozole. Starting from the second week of treatment, mice were subjected to daily evaluations of the progression of their estrus cycles via vaginal smears. At the end of treatment, animals were killed and analyses were performed. Estrus cycles progressed through all phases in the negative control group; however, cycles were arrested at day 8 - 10 in treated mice of all at all concentrations and in positive controls. No abnormalities were observed regarding the gross morphology of uteri/ovaries or histology following treatment in negative control animals. Uteri of mice that received either Inositol or letrozole displayed immature/metestrus-diestrus-like aspect and small/immature ovaries. Ovaries from mice treated with 5 mg/d Inositol had normal primary and secondary follicles, but had cystic tertiary follicles. Ovaries of letrozole-treated mice were similar, but contained larger cystic follicles, characterized by the absence of the oocyte. Ovaries of animals treated with 10 or 20 mg/d Inositol had some primary and secondary follicles, a very limited number of tertiary follicles, no follicles at more advanced stages, and no cystic follicles. In addition, animals treated with 10 or 20 mg/d Inositol displayed areas with diffused, aberrant cell proliferation. Levels of serum testosterone in the 5 mg/d treated group was statistically significantly increased compared to negative control mice ($p < 0.05$). Levels of serum testosterone in higher dose groups were similar or lower than those of negative control mice. Levels of aromatase in the ovaries of mice treated with 5 mg/d was statistically significantly lower compared to the positive control ($p < 0.05$), and lower than the negative control (not statistically significant). Serum aromatase levels were statistically significantly lower in the 5 mg/d treated group compared to positive and negative controls. No significant differences were observed in higher dose groups compared to positive and negative controls.

Groups of 6 Long Evans female rats were given diets containing 0 or 1% of an inositol (isomer unspecified) for 37 d prior to mating with untreated males.[80] Pup growth, reproduction, and lactation parameters were evaluated. No significant difference in the rate of growth or gross appearance were observed in dams treated with an inositol versus the untreated control group. Similarly, no significant difference in the number of pups/litter was observed in control and treated groups. Lactation was inadequate in both control and treated groups; however, this effect was likely due to dietary fat insufficiencies. No other details regarding this study were provided.

Other

The effect of Inositol (as *myo*-inositol) on post-implantation/post-natal development was evaluated in fertilized C57BL/6N mouse embryos in vitro (number of embryos analyzed not stated).[81] Naturally-fertilized, one-cell embryos were cultured with either 14 µl/ml Inositol in cleavage medium or phosphate-buffered saline in cleavage medium. Developing embryos were scored daily for morphology and progression through cleavage stages. Embryos of the blastocyst or morula

stage were analyzed for activation of the protein kinase B (PKB)/Akt pathway (known to modulate proliferation/survival cellular processes) via immunofluorescence analysis. The level of serine 473-phosphorlayed Akt did not appear to be modified in embryos cultured in the presence of Inositol in the morula stage; however, it was increased at the blastocyst stage, compared to untreated controls ($p = 0.02$). In 10 replicate experiments, embryos that developed to the blastocyst stage after 4 d of culture with or without Inositol were transferred to the uteri of untreated, pseudopregnant mice (number of animals used not specified). On the day of delivery, newborn animals were weighed, checked for gross abnormalities, and left to be nursed until weaning. The number of delivered animals was statistically-significantly increased in embryos treated with Inositol compared to untreated controls ($p < 0.05$). Somatometric development and body weights at birth, 1 wk, and 3 wk after birth were similar in control and treated embryos.

GENOTOXICITY STUDIES

Details regarding the QSAR models summarized below can be found in Table 4.

The mutagenic potential of Inositol (as *myo*-inositol) was evaluated in several QSAR models (prediction of Ames assay, chromosomal aberration assay, in vitro mouse lymphoma assay, and in vivo micronucleus assay).[4] The test substance was predicted to be non-genotoxic in all models.

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the literature, and no unpublished data were submitted.

ANTI-CARCINOGENICITY STUDIES

Inositol has been observed to have statistically-significant anti-carcinogenic/tumor suppressive effects in vitro (in colorectal cell lines treated with Inositol (as *myo*-inositol) at up to 5%), in mice (orally-administered Inositol (as *myo*-inositol) at 1 - 3%), in humans (smokers orally-administered 18 g/d Inositol (as *myo*-inositol)), and in a case report in which a patient with metastatic melanoma consumed a daily dietary supplement consisting of phytic acid and inositol (isomer unspecified; dose taken not stated).[82-89] Other studies performed in mice report that Inositol (as *myo*-inositol) supplementation does not have a statistically-significant effect on tumor suppression (studies performed using orally-administered Inositol at 0.5 and 3%).[90-92]

OTHER RELEVANT STUDIES

Neurotoxicity

The following study has been provided as it may provide information regarding the potential neurotoxicity of Inositol. The effect of Inositol (as *myo*-inositol) on the proliferation of cultured Schwann cells was evaluated in vitro.[93] Schwann cells were isolated from the sciatic nerve of neonatal Sprague-Dawley rats and cultured with Inositol (50 – 100 µg/ml) for 24 h. Proliferation was estimated with incorporation of tritiated thymidine into DNA synthesis (experiments carried out 3 – 4 times). To determine if Inositol inhibits axolemma-stimulated proliferation of Schwann cells, axolemma was added at various concentrations to the cell culture medium. The test substance inhibited incorporation of tritiated thymidine into DNA synthesis in a dose-dependent manner (suggesting inhibitory effect on Schwann cell proliferation). In addition, Inositol also inhibited axolemma-stimulated proliferation of Schwann cells with concentrations of axolemma ranging from 1 – 16 µg protein equivalent axolemma/well.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

The dermal irritation potential of Inositol (as *myo*-inositol; 0.1 g) was evaluated in 5 albino Hartley guinea pigs.[4] The test substance was moistened with physiological saline to improve contact with skin, and applied to normal and abraded skin under occlusive conditions (24-h exposure). Irritation reactions were observed at 3, 24, and 48 h after patch removal. Control animals were treated according to the same protocol, with physiological saline only (number of animals used in control group not stated). No irritation was observed in any of the groups. The primary irritation index was determined to be 0.

Sensitization

A guinea pig maximization assay was performed to evaluate the sensitization potential of Inositol (as *myo*-inositol).[4] Test and control groups consisted of 10 and 5 female Dunkin-Hartley guinea pigs, respectively. Animals were sensitized with 3 intradermal injections consisting of 50% adjuvant and 50% physiological saline, a 10% solution of Inositol in physiological saline, and a 20% solution of Inositol in physiological saline and adjuvant. Control animals were treated with water in place of Inositol. Seven days after sensitization, a 60% solution of Inositol in water was intracutaneously applied to injection sites under a closed patch for 48 h. (Control animals were again treated with water.) Animals were challenged on day 21 after initiation of sensitization with either 30, 60, or 100% Inositol (aqueous solutions; 24-h closed patch). Skin reactions were evaluated 24 and 48 h after patch removal. The test substance was considered to be non-sensitizing.

OCULAR IRRITATION STUDIES

In Vitro

A reconstructed human cornea-like epithelium test was performed using EpiOcular tissues according to Organisation for Economic Cooperation and Development (OECD) test guidelines (TG) 492.[4] Tissues were incubated with either the test substance (Inositol (as *myo*-inositol), 97.9% purity; 50 mg; no vehicle), the positive control (50 µl methyl acetate), or the negative control (50 µl sterile deionized water), for 6 h. All tissues were tested in duplicate. The test substance was determined to be a non-irritant (mean viability of 92.2%). Positive and negative controls gave expected results.

CLINICAL STUDIES

Effects Observed with Use of Inositol for Disease/Disorder Treatment

A review article was found in the literature summarizing available data on the use of Inositol (as *myo*-inositol) for the treatment and prevention of pathological changes associated with disease (e.g., polycystic ovary syndrome, diabetes, cancer, erectile dysfunction, psoriasis, Alzheimer's, depression, panic disorder, bulimia nervosa, obsessive-compulsive disorder) in adults.[94] According to the review, adverse effects related to Inositol treatment at a dose of 12 g/d or higher include nausea, flatus, loose stools, and diarrhea. The severity of these effects did not increase with higher doses (30 g/d). At a dose of 4 g/d, Inositol usage did not cause adverse effects.

Studies performed in pregnant women (4 g Inositol (as *myo*-inositol)/d throughout pregnancy) was not associated with side effects or increased risk of adverse effects of pregnancy.[95] However, in a meta-analysis evaluating the effect of supplementation with an inositol (isomer unspecified) on the incidence of retinopathy of prematurity, a trend towards increased mortality was observed in infants treated with the inositol versus infants in the placebo group; however, this effect was not statistically significant.[96] In a limited number of psychiatric patients, mild neurological discomfort (e.g., insomnia, dizziness) was observed following treatment with Inositol (as *myo*-inositol).[18] Three cases of mania were reported in the literature following the use of an inositol (isomer unspecified) in patients with mental health disorders; symptoms subsided following lowering or cessation of inositol usage.[97] In a study in which Inositol (as D-*chiro*-inositol; 1200 mg/d) was given orally to 20 insulin-resistant women for 6 mo, serum estradiol increases and menstrual abnormalities were observed.[78]

Effect of Inositol on Reproductive Dysfunction

Eighty-six idiopathic infertile couples were observed in a study evaluating the effect of a Inositol (as *myo*-inositol) vaginal suppository on sperm motility, cervical mucus quality, and pregnancy rate.[98] In all cases of pregnancy, evaluations of gestational progress and fetal health were performed to confirm safety of treatment. Forty-three couples were treated with the Inositol vaginal suppositories, while the remaining 43 couples received placebo suppositories. Both groups underwent 1 - 3 consecutive cycles of treatment (each cycle consisted of using 3 suppositories, one every other day, during periovulatory time, prior to bedtime). Sperm analyses were performed before the first cycle of treatment, and 3 - 6 h post-coitus (following last suppository application). Treatment with Inositol improved total sperm motility (54.42 ± 8.72) when compared to either baseline (46.48 ± 4.05) and to the placebo group (46.21 ± 5.33). Inositol treatment resulted in mild improvement of cervical mucus quality, reducing viscosity, spinnbarkeit, and ferning. In addition, treatment with Inositol resulted in an increased pregnancy rate (18.60% pregnancy rate in Inositol-treated couples; 6.97% pregnancy rate in placebo-treated couples). Pregnancies in Inositol-treated couples were evaluated via ultrasound investigation at 12, 22, and 32 wk, and newborns were subjected to evaluation 7 - 10 d after birth. No adverse effects were observed in mothers or fetuses/newborns.

Ten male volunteers aged between 30 - 65 yr, with a BMI between 22 and 34 and moderate alteration of glycemia and/or testosterone and estradiol levels, were instructed to take Inositol (as D-*chiro*-inositol; 1 g) supplements, orally, for 1 mo.[99] Serum assays for evaluated parameters (testosterone, droepiandrosterone sulfate, estradiol, follicle-stimulating hormone, luteinizing hormone, glycemia, insulinemia, inhibin B, and epiandrosterone) were evaluated at baseline and after treatment. Supplementation was associated with reduced levels of estrone (-85%) and estradiol (-14.4%) and increased levels of testosterone (+23.4%), dehydroepiandrostrone (+13.8%), and epiandrosterone (+39%). A non-statistically significant decrease in glycemia and insulinemia were observed following treatment. Other evaluated parameters were similar before and after treatment. No adverse effects were observed throughout treatment.

The effect of two isomers of Inositol (*myo*-inositol and D-*chiro*-inositol) on ovarian dysfunction was evaluated in female long-term lymphoma survivors (average age of 34 yr; 45 females/group) in a pilot prospective case-control study.[100] Treated patients were given an oral supplement of 400 mg *myo*-inositol and 45 mg D-*chiro*-inositol, 3 times per day, for 12 mo. Controls were left untreated. Levels of follicle-stimulating hormone, luteinizing hormone, progesterone, 17-β estradiol, and anti-Müllerian hormone were evaluated at baseline and following treatment. Antral follicle counts and menstrual frequency was also evaluated. Statistically-significant reductions in follicle-stimulating hormone, luteinizing hormone, and oligomenorrhea were observed in treated patients compared to baseline. Antral follicle counts of the right ovary was significantly increased in treated patients compared to baseline. When comparing untreated and treated patients, after 12 mo of treatment, a statistically-significant higher mean value in follicle-stimulating hormone and luteinizing hormone and a statistically-significant lower mean antral follicle count value in the right ovary were observed in untreated patients compared to treated patients. In addition, a statistically-significant increase in dyspareunia and dysmenorrhea were observed in

untreated patients compared to treated patients. No other evaluated parameters were significantly different between treated and untreated groups.

The effect of Inositol (as D-*chiro*-inositol) on sperm motility (evaluated as mitochondrial membrane potential (MMP)) was evaluated in patients with and without asthenozoospermia.[101] Semen samples from 15 patients with asthenozoospermia and 15 healthy patients were incubated with increasing concentrations of Inositol (0, 75, and 750 µg/ml) for 30 min. Flow cytometric analyses were performed and mitochondrial membrane potential was observed. Inositol decreased the percentage of spermatozoa with low MMP in both normozoospermic men and patients with asthenozoospermia in a concentration-dependent manner ($p < 0.005$), compared to untreated control samples (suggesting improved sperm motility).

Topical Application of D-*chiro*-Inositol in Patients with Plaque Psoriasis

A placebo-controlled, double-blind study was performed to evaluate the clinical effects of topically-applied Inositol (as D-*chiro*-inositol) on mild plaque psoriasis (46 psoriatic patients and 10 healthy subjects).[28] Three stable psoriatic plaques were selected for evaluation for each patient. Lesions were treated with different samples (i.e., medium without active agent, 0.25% Inositol, or 1% Inositol; 1 fingertip unit per lesion) twice a day. Test preparations also contained rapeseed, hemp, and flaxseed oils. Patients were evaluated at baseline, after 3 wk of treatment, after 6 wk of treatment, and 2 wk after the 6-wk treatment period. No patients complained of irritation, dryness, or allergic reactions of treated regions throughout the study.

Retrospective and Multicenter Studies

A randomized, double-masked, multi-center study was performed to evaluate the safety of treatment with an inositol (isomer unspecified) in premature infants (n = 122, 14 centers (number of infants per group not stated)).[102] Infants were treated with placebo (5% glucose) or with 8, 10, or 40 mg/kg/d inositol. Dosing was performed intravenously and converted to enteral when feedings were established. Once feedings were established, dosing occurred for either 10 wk chronological age, or up to 34 wk postmenstrual age, death, or discharge. Adverse events (cardiopulmonary, gastrointestinal, hematological, metabolic, renal, and respiratory effects) were monitored from 24 h prior to drug administration until 7 d after final dose administration. Adverse events and co-morbidities were fewer in the inositol-treated group compared to the placebo-treated group (but not statistically-significantly so).

SUMMARY

The safety of Inositol as used in cosmetics is reviewed in this safety assessment. Inositol is reported to function in cosmetics as a hair-conditioning agent and humectant.

According to 2023 VCRP data, Inositol is used in 212 total formulations (185 leave-on formulations and 27 rinse-off formulations). This ingredient is reported to be used at up to 2% in face and neck product and in moisturizing products.

More than 98% of total ingested Inositol (as D-*chiro*-inositol) was absorbed from the gastrointestinal tract in an assay in which animals were given a diet containing 0.23% Inositol for at least 1 mo plus 1 wk. The mean serum concentrations of 3 groups of rats given 2 g/kg Inositol (as *myo*-inositol) in distilled water were 54.4, 43.9, and 44.6 µg/ml. Supplementation of the diet of pregnant rats with 0.5% Inositol (as *myo*-inositol) resulted in increased levels of Inositol in the plasma, liver, kidneys, and intestines of offspring, and increased levels of Inositol in the milk and mammary tissues of dams. A maximum plasma concentration of 0.23 mM was observed in 8-d-old rats given a formula supplemented with 114 mg/100 ml Inositol (as *myo*-inositol). In a study performed in 5 female subjects given 100 mg/kg bw Inositol (as *myo*-inositol) in water (oral ingestion), the highest urinary Inositol concentration was approximately 550 µmol/mmol creatinine 275 min after test substance administration. Mean C_{max} values in subjects administered a soft gel containing 600 g Inositol, 2000 mg of Inositol powder, a soft gel containing 1200 mg Inositol, and 4000 mg of Inositol powder were 31.5, 36.3, 41.5 and 45 µmol/l, respectively (soft gels and powders contained the isomer *myo*-inositol).

An acute oral LD_{50} of 10,000 mg/kg bw was established for Inositol (as *myo*-inositol) in an acute oral toxicity assay performed in mice. QSAR analysis of Inositol (as *myo*-inositol) resulted in a predicted acute oral LD_{50} of 19,483.68 mg/kg myo-inositol (in rats).

No significant differences in weight gain and patterns of lipids in the liver were observed in male Wistar rats of different ages (20-d-old and 3-mo-old) given Inositol (as *myo*-inositol; up to 1000 mg/kg bw/d in 20-d-old rats and up to 5000 mg/kg bw/d in 3-mo-old rats) via gavage for 3 mo, compared to controls. No adverse effects relating to hormone levels, BMI, insulinemia, and insulin resistance were observed in 10 healthy women given 1200 mg Inositol (as D-*chiro*-inositol) once daily for 1 mo; however, increased testosterone and asprosin levels were observed. No alerts for short-term oral toxicity or organ toxicity were raised for Inositol (as *myo*-inositol) using QSAR analysis.

Altered ovarian histology, and a statistically-significant increase in serum testosterone and statistically-significant decrease in aromatase were apparent in mice given Inositol (as D-*chiro*-inositol) in amounts of 5 mg/d in drinking water for 21 d. No test substance-related adverse developmental or reproductive effects were observed in offspring in an assay in which female rats were treated with 1% of an inositol (isomer unspecified) for 37 d prior to mating with untreated males. An increase in the number of delivered animals (compared to controls) and normal somatometric development was observed in

mouse pups that were cultured with 14 µl/ml Inositol (as *myo*-inositol) in the embryo stage prior to the implantation into the uteri of pseudopregnant untreated mice.

The mutagenic potential of Inositol (as *myo*-inositol) was evaluated in several QSAR models (prediction of Ames assay, chromosomal aberration assay, in vitro mouse lymphoma assay, and in vivo micronucleus assay). The test substance was predicted to be non-genotoxic in all models.

Inositol (as *myo*-inositol) has been observed to have statistically-significant, anti-carcinogenic/tumor suppressive effects in vitro and in vivo. Conversely, some studies performed in mice report that Inositol (as *myo*-inositol) supplementation does not have a statistically-significant effect on tumor suppression.

Inositol (as *myo*-inositol; 50 – 100 µg/ml) resulted in a dose-dependent inhibited proliferation of Schwann cells in an in vitro assay. The test substance also inhibited axolemma-stimulated proliferation of Schwann cells.

No irritation was observed in a dermal irritation assay in which moistened Inositol (as *myo*-inositol; 0.1 g) was applied to the normal and abraded skin of 5 guinea pigs under occlusive conditions (24-h exposure). Inositol (as *myo*-inositol) was determined to be non-sensitizing in a guinea pig maximization assay (intradermal injection induction: 10 - 20% Inositol; intracutaneous induction: 60% Inositol (48-h closed patch); challenge: 30 - 100% Inositol (24-h closed patch).

Inositol (as *myo*-inositol) was considered to be a non-irritant in an EpiOcular assay in which tissues were incubated with 50 mg Inositol for 6 h. The mean tissue viability was reported to be 92.2%.

Inositol has been reported to be used as a dietary supplement for the treatment of various illnesses. Adverse effects reported following use as an oral supplement include gastrointestinal issues (at doses of 12 g/d or higher), mild neurological discomfort, menstrual abnormalities, and mania in case reports in several individuals with mental health disorders. A trend towards increased mortality was observed in a meta-analysis evaluating the effect of inositol (isomer unspecified) supplementation in infants; however, this effect was not statistically significant.

An increased pregnancy rate (18.60%) compared to placebo-treated controls (6.97%) was observed in study in which 86 idiopathic couples were given an Inositol (as *myo*-inositol) vaginal suppository or a placebo suppository to evaluate the effect of Inositol on fertility parameters. Reduced levels of estrone, estradiol, and increased levels of testosterone, dehydroepiandrostrone, and epiandrosterone were observed in an assay in which 10 male volunteers were given Inositol (as D-*chiro*-inositol) as an oral supplement for 1 mo. The effect of an oral supplement containing 400 mg *myo*-inositol and 45 mg D-*chiro*-inositol (taken 3x/d for 12 mo) on ovarian dysfunction was evaluated in long-term female lymphoma survivors. When comparing untreated and treated patients, after 12 mo of treatment, a statistically-significant higher mean value in follicle-stimulating hormone and luteinizing hormone, and a statistically-significant lower mean antral follicle count value in the right ovary were observed in untreated patients compared to treated patients. Improved MMP was observed in the sperm samples of normozoospermic men and patients with asthenozoospermia when sperm was incubated with Inositol (as D-*chiro*-inositol for 30 min).

The effect of topically applied Inositol (as D-*chiro*-inositol (0.25 or 1%)) on psoriasis plaques was evaluated in 46 psoriatic patients and 10 healthy volunteers. No patients complained of irritation, dryness, or allergic reactions of treated regions throughout the study.

A multi-center study was performed to evaluate the safety of treatment with an inositol (up to 40 mg/kg/d; intravenous treatment converted to enteral when feedings established; isomer unspecified) in 122 premature infants. Treatment was not associated with increased adverse effects.

INFORMATION SOUGHT

The following information on Inositol is being sought for use in the resulting safety assessment:

- confirmation of which isomers of Inositol are used in cosmetic formulations (accordingly, all data received should be on a stereoisomer that is used in cosmetics)
- dermal absorption/dermal penetration data
- confirmatory sensitization data at the maximum reported use concentration

TABLES

Table 1. Chemical properties

Property	Value	Reference
	***myo*-Inositol**	
Physical Form	solid	[4]
Odor	odorless	[8]
Color	white	[4]
Molecular Weight (g/mol)	180.16	[6]
Density (g/cm^3@ 20ºC)	1.752	[4]
Vapor Pressure (mm Hg)	≥ 7.606 - ≤ 20.079	[4]
Melting Point (ºC)	225 - 227	[4]
Boiling Point (ºC)	384.72	[4]
Water Solubility (g/100 g water @ 60ºC)	28	[4]
log K_{ow}	-2.08	[4]
	D-*chiro*-Inositol	
Physical Form	solid	[9]
Color	white to off-white	[9]
Molecular Weight (g/mol)	180.16	[7]
Density	1.28 (estimated)	[9]
Melting Point (ºC)	230	[9]
Boiling Point (ºC)	232.96 (estimated)	[9]
Water Solubility (g/L @ 11ºC)	403.4	[9]
log K_{ow}	-2.60	[7]

Table 2. Frequency (2023) and concentration (2022) of use according to likely duration and exposure and by product category[20,21]

	# of Uses	Max Conc of Use (%)
Totals*	**212**	**0.000025 – 2**
summarized by likely duration and exposure**		
Duration of Use		
Leave-On	*185*	*0.001 – 2*
Rinse-Off	*27*	*0.00025 – 1*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type*		
Eye Area	20	1
Incidental Ingestion	1	NR
Incidental Inhalation-Spray	91[a]; 54[b]	NR
Incidental Inhalation-Powder	1; 54[b]	0.001 – 2[c]
Dermal Contact	194	0.00067 – 2
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	17	0.000025
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	4	0.00067
Baby Products	NR	NR
as reported by product category		
Eye Makeup Preparations		
Eye Shadow	7	NR
Eye Lotion	8	1
Other Eye Makeup Preparations	5	NR
Hair Preparations (non-coloring)		
Hair Conditioner	5	0.000025
Shampoos (non-coloring)	5	NR
Tonics, Dressings, and Other Hair Grooming Aids	2	NR
Other Hair Preparations	5	NR
Makeup Preparations		
Face Powders	1	NR
Foundations	2	NR
Lipstick	1	NR
Makeup Bases	2	0.001
Personal Cleanliness Products		
Bath Soaps and Detergents	3	0.00067
Shaving Preparations		
Shaving Cream	3	NR
Skin Care Preparations		
Cleansing	9	0.001 – 0.0025
Face and Neck (exc shave)	44	0.001 – 2
Body and Hand (exc shave)	10	0.001 – 0.3
Moisturizing	76	0.001 – 2
Night	8	NR
Paste Masks (mud packs)	2	1
Skin Fresheners	4	NR
Other Skin Care Preparations	9	NR
Suntan Preparations		
Other Suntan Preparations	1	NR

NR – not reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 3. Oral ADME studies

Parameter Measured	Inositol Isomer	Animals	No./Group	Vehicle/Dose	Dose/Protocol	Results	References
				ANIMAL			
Absorption and Excretion	D-*chiro*-inositol	Male Sprague-Dawley rats	3	diet containing 0.23% D-*chiro*-inositol	Animals fed diet containing a mean amount of 12.94 nmol/mg Inositol for at least 1 mo, then housed in metabolic cages and fed diet for 1 wk; urine and feces collected for 24 h (study does not state when 24 h collection period occurred). The mean intake of D-*chiro*-inositol was 921 µmol/kg bw/d.	More than 98% of the total ingested Inositol was absorbed from the gastrointestinal tract. The mean total amount of D-*chiro*-inositol found in the stool and urine was 6.2 and 42.3 µmol/kg bw/d, respectively; these minimal amounts suggest that the bulk of the ingested D-*chiro*-inositol was metabolized.	[74]
Metabolism	*myo*-inositol	Male Wistar rats	3/group	2000 mg/kg in distilled water	Animals treated via gavage; blood samples taken at different time intervals up to 48 h post-administration as follows: Group 1: 0, 0.25, 0.5, 1, 24 h Group 2: 0, 2, 4, 8, 12, 24 h Group 3: 0, 1.5, 36, 48 h	The highest mean Inositol concentration in serum samples was observed within the first hour after administration in all test animals. Concentration of the test substance in samples decreased after the maxima peak; however, after 24 h, levels were still higher than baseline. The biological half-life was determined to be 4.08 h. The mean concentrations of *myo*-inositol in groups 1, 2, and 3 were determined to be 54.4, 43.9, 44.6 µg/ml, respectively.	[17]
Distribution	*myo*-inositol	Pregnant female Holtzman rats	35/group	0.5% in diet	On 7th day of gestation, animals were divided into 2 groups and given either a purified diet with or without 0.5% Inositol for 120 d (during gestation and lactation); pups were fed corresponding diet after weaning until 3 mo of age; free *myo*-inositol content of tissues, amniotic fluid, milk, and plasma was measured via gas-liquid chromatography; lipid-bound Inositol in the form of phosphatidylinositol was quantified via a lipid extract of tissue	Supplementation of the diet with Inositol significantly increased the levels of Inositol in plasma, liver, kidney, and intestine of pups at all ages examined, and significantly increased the levels of Inositol in the milk and mammary tissue during lactation.	[75]
Distribution	*myo*-inositol	Neonatal Holtzman rats	4/sex/group	gastric intubation: 114 mg/100 ml formula (supplemented formula) 7.44 mg/100 ml formula (restricted formula) supplemented diet: 250 mg/100 g diet (Inositol content of Inositol-restricted diet not stated)	6-d-old rat pups fed liquid formula via stomach tube using either a Inositol-restricted formula, or a Inositol supplemented formula (pups fed 0.3 ml formula/g bw every 4 h); at 16 d of age, pups fed Inositol restricted formula were fed purified diet deficient in *myo*-inositol, and pups fed Inositol supplemented formula were fed an identical diet supplemented with Inositol until 72 d of age; tissues obtained and observed at selected ages (from 6- to 72-d-old) of each dietary group; blood removed via cardiac puncture	Plasma Inositol levels of animals fed the Inositol restricted formula and diet were significantly lower ($p < 0.05$) than those of Inositol supplemented rats at all ages except at day 72 d. The maximum plasma concentration of Inositol was approximately 0.23 mM (in 8-d-old Inositol supplemented rat). Most tissues (testes, kidneys, liver) examined from rats fed the Inositol-deprived formula and diet had lower free Inositol levels compared to tissues of the Inositol supplemented group, excluding the cerebrum and cerebellum. Differences between Inositol levels in testis, lens, and kidney were significant ($p < 0.05$) for 6 versus 18 d of age within each dietary group (increased amounts in older rats).	[76]

Table 3. Oral ADME studies

Parameter Measured	Inositol Isomer	Animals	No./Group	Vehicle/Dose	Dose/Protocol	Results	References
				HUMAN			
Distribution and Excretion	*myo*-inositol	Human subjects	5 females	100 mg/kg bw; aqueous solution	Baseline measurements of Inositol via blood sample taken prior to treatment; subjects ingested test substance and blood was drawn 20, 40, 60, 90, 180, and 270 min after ingestion; urine samples taken 0, 180, and 270 min after ingestion	After ingestion, mean serum concentration of *myo*-inositol increased from 19.9 µmol/l to a maximum of 96.5 µmol/l after 90 min; observed mean concentrations decreased to 77.3 µmol/l after 270 min; the highest urinary *myo*-inositol concentration was approximately 550 µmol/mmol creatinine 275 min after administration	[77]
Absorption	*myo*-inositol	Human subjects	20 total (8 males and 12 females)	Phase 1: soft gel capsule containing 600 mg Inositol Phase 2: 2000 mg Inositol powder Phase 3: soft gel capsule containing 1200 mg Inositol Phase 4: 4000 mg Inositol powder	Patients were treated with each of the test substances orally, in phases. Each phase was separated by a washout period of 15 d. Pharmacokinetic parameters were evaluated based on the analysis of Inositol plasma concentrations. Blood samples collected at baseline, 30, 60, 90, 120, 180, 300, 420, 540, and 1440 min post-administration.	Mean C_{max}: -soft gel containing 600 mg Inositol: 31.5 µmol/l -2000 mg Inositol powder: 36.3 µmol/l -soft gel containing 1200 g Inositol: 41.5 µmol/l -4000 mg Inositol powder: 45 µmol/l Mean T_{max}: -soft gel containing 600 mg Inositol: 180 min -2000 g Inositol powder: 180 min -soft gel containing 1200 mg Inositol: 120 min -4000 mg Inositol powder: 122 min	[2]

C_{max} = maximum observed plasma concentration; T_{max} = time to peak concentration

Table 4. QSAR models evaluating genotoxicity[4]

Inositol Isomer	Test System	Procedure	Results
myo-inositol	*S. typhimurium* strains TA 102, TA 100, TA 98, TA 1537, TA 1535	QSAR – Ames assay prediction; with metabolic activation; Times v.2.27.19.13 in QSAR Toolbox	No mutagenic potential predicted
myo-inositol	*S. typhimurium* strains TA 102, TA 100, TA 98, TA 1537, TA 1535	QSAR – Ames assay prediction; without metabolic activation; Times v.2.27.19.13 in QSAR Toolbox	No mutagenic potential predicted
myo-inositol	Chinese hamster ovary and lung cells	QSAR – in vitro cytogenicity/chromosome aberration assay prediction; with metabolic activation; Times v.2.27.19.13 in QSAR Toolbox	No mutagenic potential predicted
myo-inositol	Chinese hamster ovary and lung cells	QSAR – in vitro cytogenicity/chromosome aberration assay prediction; without metabolic activation; Times v.2.27.19.13 in QSAR Toolbox	No mutagenic potential predicted
myo-inositol	NR	QSAR – in vitro mouse lymphoma assay prediction; with and without metabolic activation; OASIS TIMES v.2.31.2.82	No mutagenic potential predicted
myo-inositol	Mammalian erythrocytes and peripheral blood	QSAR – in vivo micronucleus assay prediction; Times v.2.27.19.13 in QSAR Toolbox	No mutagenic potential predicted

NR = not reported; QSAR = quantitative structure activity relationship

REFERENCES

1. Nikitakis J, Kowcz A. wINCI: *International Cosmetic Ingredient Dictionary and Handbook*. http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC: Personal Care Products Council. Last Updated 2024. Accessed March 1, 2024.

2. Carlomagno G, De Grazia S, Unfer V, Manna F. *myo*-Inositol in a new pharmaceutical form: a step forward to a broader clinical use. *Expert Opin Drug Deliv*. 2012;9(3):267-271.

3. Siracusa L, Napoli E, Ruberto G. Novel chemical and biological insights of inositol derivatives in mediterranean plants. *Molecules*. 2022;27(5):1525.

4. European Chemicals Agency (ECHA). myo-Inositol. https://echa.europa.eu/da/registration-dossier/-/registered-dossier/24300/4/3. Last Updated 2023. Accessed August 28, 2023.

5. Chhetri DR. *myo*-Inositol and its derivatives: Their emerging role in the treatment of human diseases. *Front Pharmacol*. 2019;10:1172.

6. PubChem. Inositol. https://pubchem.ncbi.nlm.nih.gov/compound/Inositol. Last Updated 2023. Accessed August 28, 2023.

7. The Human Metabolome Database. Metabocard for D-*chiro*-Inositol. https://hmdb.ca/metabolites/HMDB0240209. Last Updated Accessed March 27, 2024.

8. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). Scientific opinion on the safety and efficacy of inositol as a feed additive for fish, dogs, and cats. *EFSA Journal*. 2014;12(5).

9. Chemical Book. D-*chiro*-Inositol. https://www.chemicalbook.com/ChemicalProductProperty_EN_CB0718693.htm. Last Updated 2024. Accessed March 27, 2024.

10. Li Y, Han P, Wang J, Shi T, You C. Production of myo-inositol: recent advance and prospective. *Biotechnol Appl Biochem*. 2022;69(3):1101-1111.

11. Chung SK, Kwon YU. Practical synthesis of all inositol stereoisomers from myo-inositol. *Bioorg Med Chem Lett*. 1999;9(15):2135-2140.

12. Thomas MP, Mills SJ, Potter BV. The "other" inositols and their phosphates: Synthesis, biology, and medicine (with recent advances in myo-inositol chemistry). *Angew Chem Int Ed Engl*. 2016;55(5):1614-1650.

13. United States Pharmacopeial Convention. Food Chemicals Codex. 2023: https://www.foodchemicalscodex.org/.

14. Phelps DL, Ward RM, Williams RL, et al. Pharmacokinetics and safety of a single intravenous dose of myo-inositol in preterm infants of 23-29 wk. *Pediatr Res*. 2013;74(6):721-729.

15. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). Safety and efficacy of inositol as nutritional additive for dogs and cats. *EFSA Journal*. 2016;16(6):e4511.

16. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific Opinion on the substantiation of health claims related to inositol and cognitive function (ID 1588) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2009.1304. Last Updated 2009. Accessed March 26, 2024.

17. Antonowski T, Osowski A, Szczesny D, et al. Pharmacokinetics of myo-inositol in a wistar rat animal model. *Int J Mol Sci*. 2022;23(19):11246.

18. Bizzarri M, Fuso A, Dinicola S, Cucina A, Bevilacqua A. Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease. *Expert Opin Drug Metab Toxicol*. 2016;12(10):1181-1196.

19. Gambioli R, Montanino Oliva M, Nordio M, Chiefari A, Puliani G, Unfer V. New insights into the activities of d-chiro-inositol: A narrative review. *Biomedicines*. 2021;9(10):1378.

20. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2023. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" 2023; received February 2, 2023).

21. Personal Care Products Council. 2022. Concentration of Use by FDA product category: Inositol. Unpublished data submitted to Personal Care Products Council on July 6, 2022.

22. EUR-Lex. Access to European Union Law. https://eur-lex.europa.eu/homepage.html. Last Updated 2024. Accessed February 8, 2024.

23. Wang J, Cheng H, Zhao Z, Zhang Y. Efficient production of inositol from glucose via a tri-enzymatic cascade pathway. *Bioresour Technol*. 2022;353:127125.

24. Kiani AK, Paolacci S, Calogero AE, et al. From myo-inositol to D-chiro-inositol molecular pathways. *Eur Rev Med Pharmacol Sci*. 2021;25(5):2390-2402.

25. Clements RS, Jr., Darnell B. myo-Inositol content of common foods: development of a high-myo-inositol diet. *Am J Clin Nutr*. 1980;33(9):1954-1967.

26. U.S. Food and Drug Administration. FDA Label Search. https://labels.fda.gov/ingredientname.cfm. Last Updated 2023. Accessed January 2, 2023.

27. US Food and Drug Administration (FDA). OTC Active Ingredients. https://www.fda.gov/media/75750/download. Last Updated April 7, 2010. Accessed March 5, 2024.

28. Owczarczyk-Saczonek A, Czerwińska J, Wygonowska E, Kasprowicz-Furmańczyk M, Placek W. D-chiro-Inositol as a treatment in plaque psoriasis: a randomized placebo-controlled clinical trial. *Dermatol Ther*. 2021;34(1):e14538.

29. Wei J, Yan J, Yang H. Inositol nutritional supplementation for the prevention of gestational diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2022;14(14):2831.

30. Vitagliano A, Saccone G, Cosmi E, et al. Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. *Arch Gynecol Obstet*. 2019;299(1):55-68.

31. D'Anna R, Di Benedetto A, Scilipoti A, et al. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women: A randomized controlled trial. *Obstet Gynecol*. 2015;126(2):310-315.

32. Tahir F, Majid Z. Inositol supplementation in the prevention of gestational diabetes mellitus. *Cureus*. 2019;11(9):e5671.

33. Fraticelli F, Celentano C, Zecca IA, et al. Effect of inositol stereoisomers at different dosages in gestational diabetes: an open-label, parallel, randomized controlled trial. *Acta Diabetol*. 2018;55(8):805-812.

34. Dell'Edera D, Sarlo F, Allegretti A, Simone F, Lupo MG, Epifania AA. The influence of D-chiro-inositol and D-myo-inositol in pregnant women with glucose intolerance. *Biomed Rep*. 2017;7(2):169-172.

35. Leppink EW, Redden SA, Grant JE. A double-blind, placebo-controlled study of inositol in trichotillomania. *Int Clin Psychopharmacol*. 2017;32(2):107-114.

36. Seedat S, Stein DJ, Harvey BH. Inositol in the treatment of trichotillomania and compulsive skin picking. *J Clin Psychiatry*. 2001;62(1):60-61.

37. Chengappa KN, Levine J, Gershon S, et al. Inositol as an add-on treatment for bipolar depression. *Bipolar Disord*. 2000;2(1):47-55.

38. Mukai T, Kishi T, Matsuda Y, Iwata N. A meta-analysis of inositol for depression and anxiety disorders. *Hum Psychopharmacol*. 2014;29(1):55-63.

39. Gianfranco C, Vittorio U, Silvia B, Francesco D. myo-Inositol in the treatment of premenstrual dysphoric disorder. *Hum Psychopharmacol*. 2011;26(7):526-530.

40. Guarnieri G, Iervolino M, Cavallone S, Unfer V, Vianello A. The "asthma-polycystic ovary overlap syndrome" and the therapeutic role of myo-inositol. *Int J Mol Sci*. 2023;24(8):6959.

41. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. *Eur Rev Med Pharmacol Sci*. 2009;13(2):105-110.

42. Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. Antioxidants for female subfertility. *Cochrane Database Syst Rev*. 2017;7(7):Cd007807.

43. Facchinetti F, Appetecchia M, Aragona C, et al. Experts' opinion on inositols in treating polycystic ovary syndrome and non-insulin dependent diabetes mellitus: a further help for human reproduction and beyond. *Expert Opin Drug Metab Toxicol*. 2020;16(3):255-274.

44. Zhang JQ, Xing C, He B. Short period-administration of myo-inositol and metformin on hormonal and glycolipid profiles in patients with polycystic ovary syndrome: a systematic review and updated meta-analysis of randomized controlled trials. *Eur Rev Med Pharmacol Sci*. 2022;26(6):1792-1802.

45. Vyas L, Raiturker AP, Sud S, et al. Management of polycystic ovary syndrome among Indian women using myo-inositol and D-chiro-inositol. *Bioinformation*. 2022;18(2):103-110.

46. Lei W, Gao Y, Hu S, Liu D, Chen Q. Effects of inositol and alpha lipoic acid combination for polycystic ovary syndrome: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99(30):e20696.

47. Ramanan EA, Ravi S, Anbu KRR, Michael M. Efficacy and safety of tracnil™ administration in patients with dermatological manifestations of pcos: An open-label single-arm study. *Dermatol Res Pract*. 2020:7019126.

48. Januszewski M, Issat T, Jakimiuk AA, Santor-Zaczynska M, Jakimiuk AJ. Metabolic and hormonal effects of a combined myo-inositol and D-chiro-inositol therapy on patients with polycystic ovary syndrome (PCOS). *Ginekol Pol*. 2019;90(1):7-10.

49. Zhao H, Xing C, Zhang J, He B. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis. *Reprod Health*. 2021;18(1):171.

50. Pericuesta E, Laguna-Barraza R, Ramos-Ibeas P, et al. D-chiro-inositol treatment affects oocyte and embryo quality and improves glucose intolerance in both aged mice and mouse models of polycystic ovarian syndrome. *Int J Mol Sci*. 2020;21(17):6049.

51. Formuso C, Stracquadanio M, Ciotta L. Myo-inositol vs. D-chiro inositol in PCOS treatment. *Minerva Ginecol*. 2015;67(4):321-325.

52. Kachhawa G, Senthil Kumar KV, Kulshrestha V, Khadgawat R, Mahey R, Bhatla N. Efficacy of myo-inositol and D-chiro-inositol combination on menstrual cycle regulation and improving insulin resistance in young women with polycystic ovary syndrome: A randomized open-label study. *Int J Gynaecol Obstet*. 2022;158(2):278-284.

53. Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. myo-Inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. *Endocr Connect*. 2017;6(8):647-658.

54. Galazis N, Galazi M, Atiomo W. D-chiro-Inositol and its significance in polycystic ovary syndrome: a systematic review. *Gynecol Endocrinol*. 2011;27(4):256-262.

55. Le Donne M, Metro D, Alibrandi A, Papa M, Benvenga S. Effects of three treatment modalities (diet, myoinositol or myoinositol associated with D-chiro-inositol) on clinical and body composition outcomes in women with polycystic ovary syndrome. *Eur Rev Med Pharmacol Sci*. 2019;23(5):2293-2301.

56. Davinelli S, Nicolosi D, Di Cesare C, Scapagnini G, Di Marco R. Targeting metabolic consequences of insulin resistance in polycystic ovary syndrome by d-chiro-inositol and emerging nutraceuticals: A focused review. *J Clin Med*. 2020;9(4):987.

57. Colak E, Ozcimen EE, Tohma YA, Ceran MU. May myo-inositol and D-chiro-inositol (40:1) treatment be a good option on normal-weighted polycystic ovary syndrome patients without insulin resistance? *J Obstet Gynaecol Res*. 2020.

58. Bevilacqua A, Dragotto J, Giuliani A, Bizzarri M. myo-Inositol and D-chiro-inositol (40:1) reverse histological and functional features of polycystic ovary syndrome in a mouse model. *J Cell Physiol*. 2019;234(6):9387-9398.

59. Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of inositol(s) in women with pcos: A systematic review of randomized controlled trials. *Int J Endocrinol*. 2016:1849162.

60. La Marca A, Grisendi V, Dondi G, Sighinolfi G, Cianci A. The menstrual cycle regularization following D-chiro-inositol treatment in PCOS women: a retrospective study. *Gynecol Endocrinol*. 2015;31(1):52-56.

61. Pezza M, Carlomagno V, Casucci G. Inositol and acne. *G Ital Dermatol Venereol*. 2015;150(6):649-653.

62. Zacchè MM, Caputo L, Filippis S, Zacchè G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2009;25(8):508-513.

63. Calogero AE, Gullo G, La Vignera S, Condorelli RA, Vaiarelli A. Myoinositol improves sperm parameters and serum reproductive hormones in patients with idiopathic infertility: a prospective double-blind randomized placebo-controlled study. *Andrology*. 2015;3(3):491-495.

64. Colazingari S, Treglia M, Najjar R, Bevilacqua A. The combined therapy myo-inositol plus D-chiro-inositol, rather than D-chiro-inositol, is able to improve IVF outcomes: results from a randomized controlled trial. *Arch Gynecol Obstet*. 2013;288(6):1405-1411.

65. Nordio M, Kumanov P, Chiefari A, Puliani G. D-chiro-Inositol improves testosterone levels in older hypogonadal men with low-normal testosterone: a pilot study. *Basic Clin Androl*. 2021;31(1):28.

66. Mendoza N, Losa F, Palacios S. Strategy to improve the female fertility in the general gynecologist's office: use of a nutritional supplement based on myo-inositol/D-chiro-inositol and antioxidants. *Gynecol Endocrinol*. 2022;38(4):275-278.

67. Amabile MI, De Luca A, Tripodi D, et al. Effects of inositol hexaphosphate and *myo*-inositol administration in breast cancer patients during adjuvant chemotherapy. *J Pers Med*. 2021;11(8):756.

68. Benvenga S, Nordio M, Laganà AS, Unfer V. The role of inositol in thyroid physiology and in subclinical hypothyroidism management. *Front Endocrinol (Lausanne)*. 2021;12:662582.

69. Malvasi A, Kosmas I, Mynbaev OA, et al. Can trans resveratrol plus D-chiro-inositol and myo-inositol improve maternal metabolic profile in overweight pregnant patients? *Clin Ter*. 2017;168(4):e240-e247.

70. Gambioli R, Forte G, Aragona C, Bevilacqua A, Bizzarri M, Unfer V. The use of D-chiro-Inositol in clinical practice. *Eur Rev Med Pharmacol Sci*. 2021;25(1):438-446.

71. Pani A, Giossi R, Menichelli D, et al. Inositol and non-alcoholic fatty liver disease: A systematic review on deficiencies and supplementation. *Nutrients*. 2020;12(11):3379.

72. Li JM, Chang WH, Li L, et al. Inositol possesses antifibrotic activity and mitigates pulmonary fibrosis. *Respir Res*. 2023;24(1):132.

73. DiNicolantonio JJ, J HOK. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. *Open Heart*. 2022;9(1).

74. Lin X, Ma L, Gopalan C, Ostlund RE. D-chiro-Inositol is absorbed but not synthesised in rodents. *Br J Nutr*. 2009;102(10):1426-1434.

75. Burton LE, Wells WW. myo-Inositol metabolism during lactation and development in the rat. The prevention of lactation-induced fatty liver by dietary myo-inositol. *J Nutr*. 1976;106(11):1617-1628.

76. Burton LE, Ray RE, Bradford JR, Orr JP, Nickerson JA, Wells WW. myo-Inositol metabolism in the neonatal and developing rat fed a myo-inositol-free diet. *J Nutr*. 1976;106(11):1610-1616.

77. Groenen PM, Merkus HM, Sweep FC, Wevers RA, Janssen FS, Steegers-Theunissen RP. Kinetics of myo-inositol loading in women of reproductive age. *Ann Clin Biochem*. 2003;40(Pt 1):79-85.

78. Nordio M, Bezerra Espinola MS, Bilotta G, Capoccia E, Montanino Oliva M. Long-Lasting Therapies with High Doses of D-chiro-inositol: The Downside. *J Clin Med*. 2023;12(1):390.

79. Bevilacqua A, Dragotto J, Lucarelli M, Di Emidio G, Monastra G, Tatone C. High doses of d-chiro-inositol alone induce a pco-like syndrome and other alterations in mouse ovaries. *Int J Mol Sci*. 2021;22(11):5691.

80. Ershoff BH. Effects of massive doses of p-aminobenzoic acid and inositol on reproduction in the rat. *Proceedings of the Society for Experimental Biology and Medicine*. 1946;63(2):479-480.

81. Kuşcu N, Bizzarri M, Bevilacqua A. Myo-inositol safety in pregnancy: From preimplantation development to newborn animals. *Int J Endocrinol*. 2016:2413857.

82. Lam S, McWilliams A, LeRiche J, MacAulay C, Wattenberg L, Szabo E. A phase I study of myo-inositol for lung cancer chemoprevention. *Cancer Epidemiol Biomarkers Prev*. 2006;15(8):1526-1531.

83. Nishino H, Murakoshi M, Masuda M, et al. Suppression of lung and liver carcinogenesis in mice by oral administration of myo-inositol. *Anticancer Res*. 1999;19(5a):3663-3664.

84. Wattenberg LW, Estensen RD. Chemopreventive effects of myo-inositol and dexamethasone on benzo[a]pyrene and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone-induced pulmonary carcinogenesis in female A/J mice. *Cancer Res*. 1996;56(22):5132-5135.

85. Estensen RD, Wattenberg LW. Studies of chemopreventive effects of myo-inositol on benzo[a]pyrene-induced neoplasia of the lung and forestomach of female A/J mice. *Carcinogenesis*. 1993;14(9):1975-1977.

86. Shamsuddin AM, Ullah A, Chakravarthy AK. Inositol and inositol hexaphosphate suppress cell proliferation and tumor formation in CD-1 mice. *Carcinogenesis*. 1989;10(8):1461-1463.

87. Schröterová L, Hasková P, Rudolf E, Cervinka M. Effect of phytic acid and inositol on the proliferation and apoptosis of cells derived from colorectal carcinoma. *Oncol Rep*. 2010;23(3):787-793.

88. Khurana S, Baldeo C, Joseph RW. Inositol hexaphosphate plus inositol induced complete remission in stage IV melanoma: a case report. *Melanoma Res*. 2019;29(3):322-324.

89. Liao J, Seril DN, Yang AL, Lu GG, Yang GY. Inhibition of chronic ulcerative colitis associated adenocarcinoma development in mice by inositol compounds. *Carcinogenesis*. 2007;28(2):446-454.

90. Witschi H, Espiritu I, Ly M, Uyeminami D. The effects of dietary myoinositol on lung tumor development in tobacco smoke-exposed mice. *Inhal Toxicol*. 2004;16(4):195-201.

91. Estensen RD, Jordan MM, Wiedmann TS, Galbraith AR, Steele VE, Wattenberg LW. Effect of chemopreventive agents on separate stages of progression of benzo[alpha]pyrene induced lung tumors in A/J mice. *Carcinogenesis*. 2004;25(2):197-201.

92. Wilson MJ, Lindgren BR, Sinha AA. The effect of dietary supplementation with limonene or myo-inositol on the induction of neoplasia and matrix metalloproteinase and plasminogen activator activities in accessory sex organs of male Lobund-Wistar rats. *Exp Mol Pathol*. 2008;85(2):83-89.

93. Niwa T, Sobue G, Maeda K, Mitsuma T. Myoinositol inhibits proliferation of cultured Schwann cells: evidence for neurotoxicity of myoinositol. *Nephrol Dial Transplant*. 1989;4(7):662-666.

94. Carlomagno G, Unfer V. Inositol safety: clinical evidences. *Eur Rev Med Pharmacol Sci*. 2011;15(8):931-936.

95. Owczarczyk-Saczonek A, Lahuta LB, Ligor M, Placek W, Górecki RJ, Buszewski B. The healing-promoting properties of selected cyclitols-a review. *Nutrients*. 2018;10(12):1891.

96. Du Y, He Y, Wang YL, Zhou JG, Chen C. The efficacy and safety of inositol supplementation in preterm infants to prevent retinopathy of prematurity: a systematic review and meta-analysis. *BMC Ophthalmol*. 2019;19(1):135.

97. Levine J, Witztum E, Greenberg BD, Barak Y. Inositol-induced mania? *Am J Psychiatry*. 1996;153(6):839.

98. Montanino Oliva M, Buonomo G, Carra MC, Lippa A, Lisi F. myo-Inositol impact on sperm motility in vagina and evaluation of its effects on foetal development. *Eur Rev Med Pharmacol Sci*. 2020;24(5):2704-2709.

99. Monastra G, Vazquez-Levin M, Bezerra Espinola MS, Bilotta G, Laganà AS, Unfer V. D-chiro-Inositol, an aromatase down-modulator, increases androgens and reduces estrogens in male volunteers: a pilot study. *Basic Clin Androl*. 2021;31(1):13.

100. Dellino M, Cascardi E, Leoni C, et al. Effects of oral supplementation with myo-inositol and d-chiro-inositol on ovarian functions in female long-term survivors of lymphoma: Results from a prospective case-control analysis. *J Pers Med*. 2022;12(9):1536.

101. Condorelli RA, Barbagallo F, Calogero AE, Cannarella R, Crafa A, La Vignera S. D-chiro-inositol improves sperm mitochondrial membrane potential: In vitro evidence. *J Clin Med*. 2020;9(5).

102. Phelps DL, Ward RM, Williams RL, et al. Safety and pharmacokinetics of multiple dose myo-inositol in preterm infants. *Pediatr Res*. 2016;80(2):209-217.