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Trivalent chromium and male germ cells: current prospects and future trends

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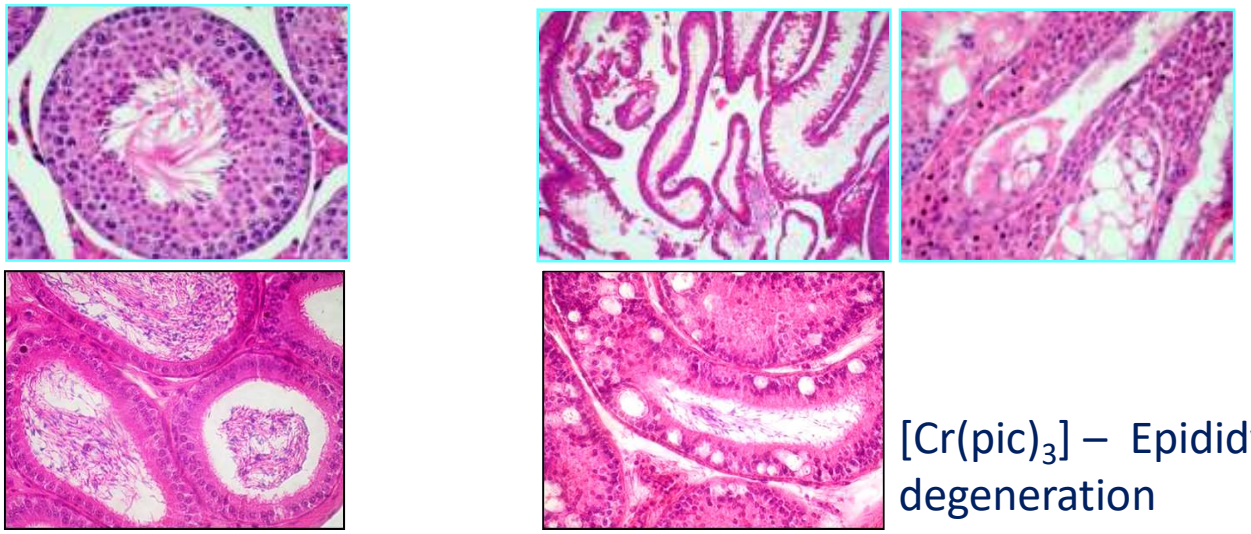
Abstract: The dietary supplement of Cr(III)-tris-picolinate, (CrPic), have been used for diabetes, body weight and muscular growth. However, its application for humans or animals has always been debatable due to contradictory results on its safety limits. Further, long-term effects of CrPic on the immunity and the antioxidant system of treated subjects have still not been properly studied. Long-term use of CrPic may prove to be carcinogenic or clastogenic. CrPic supplements are valuable for meat and poultry industries, and fertility improvement. The potential of CrPic to increase levels of certain hormones and improve the body's antioxidant status, while leaving untouched the secretion of other hormones remains underexplored. Comprehensive studies on the role of CrPic will help to establish safety. Combined with nanoparticles or biomimicking materials this may unleash a significant breakthrough for the treatment of conditions in menopausal and postmenopausal as for diseases affecting men (cardiovascular disorders and type 2 diabetes). This work encompasses a comprehensive analysis of the main benefits and risks of chromium compounds on male germ cells/male fertility. The role of this supplement in steroidogenesis and research pinpointing in vivo changes in testosterone-producing cells, spermatogenesis, and sperm quality. We will also postulate on their use to maximize male fertility.

Keywords: chromium picolinate; dietary supplements; fertility; male germ cells

Trivalent chromium and male germ cells: current prospects and future trends

Control

$[Cr(pic)_3]$ – Testis atrophy



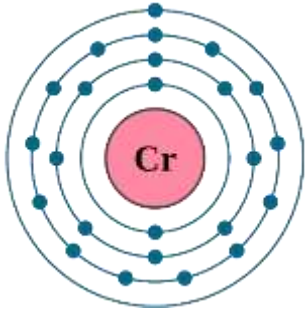
$[Cr(pic)_3]$ – Epididymis degeneration

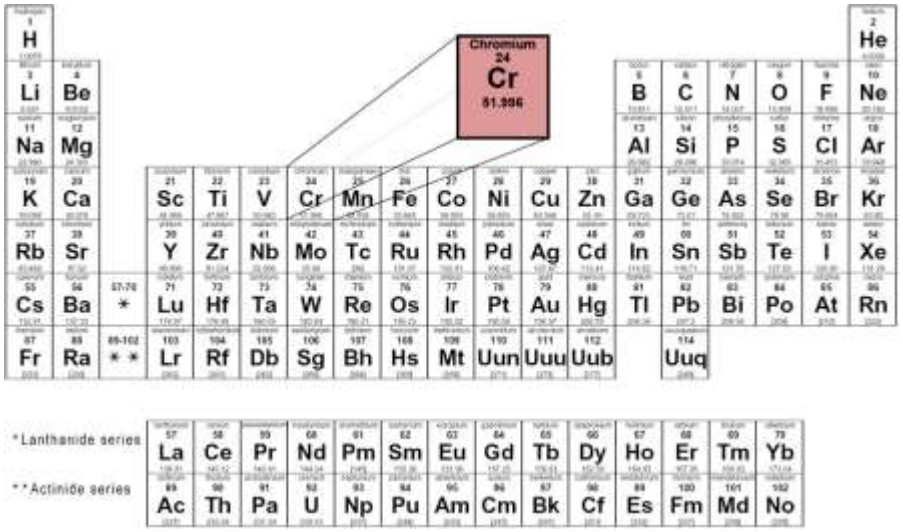
Introduction

1. CHROMIUM ESSENTIAL OR NOT?
2. Cr(III) AND TYPE 2 DIABETES
3. SUPPLEMENTS AND TOXICOLOGY
4. RELEVANCE, IMPACT AND GOALS
5. RESULTS
6. CONCLUSIONS

Introduction

Chromium exists in our environment as metallic Cr(O), trivalent Cr(III) and hexavalent Cr(VI)





Cr(III)

Relatively nontoxic due to **poor bioavailability**

Cr(VI)

Synthesized by the oxidation of Cr(III). It is a proven human **carcinogen** and environmental **pollutant**

Santos TM, Ferreira M, Pereira ML. Chromium: The Intriguing Element. What Biological Role Has It? (Cr(III)-Tris-Picolinate—Is It Safe or Not?). In: Thomas S, ed. *Microscopy Applied to Materials Sciences & Life Sciences.* Academic Press USA; 2018:427-459.

Cefalu WT, Hu FB. Role of chromium in human health and in diabetes. *Diabetes Care*. 2004;27(11):2741-2751.

Introduction

Cr(III) is studied and proposed as an essential element

1955

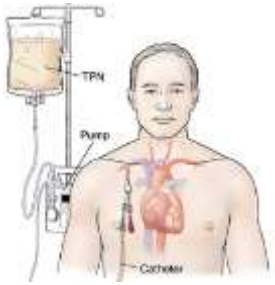
Mertz and Schwarz showed a correlation between Cr(III) and glucose

Torula yeast-based diet absent in Cr(III)

Impaired glucose tolerance reversed by adding foods rich in chromium

Chromium proposed as an essential element based on evidence from patients receiving total parenteral nutrition (TPN)

TPN solution without Cr(III)



Diabetic symptoms refractory to insulin but reversed by addition of Cr(III)

Mertz W, Schwarz K. Impaired intravenous glucose tolerance as an early sign of dietary necrotic liver degeneration. Arch Biochem Biophys. 1955;58(2):504-506.
Vincent JB. The Nutritional Biochemistry of Chromium (III). 1st ed. (Vincent JB, ed.). Elsevier Science; 2007.

Introduction

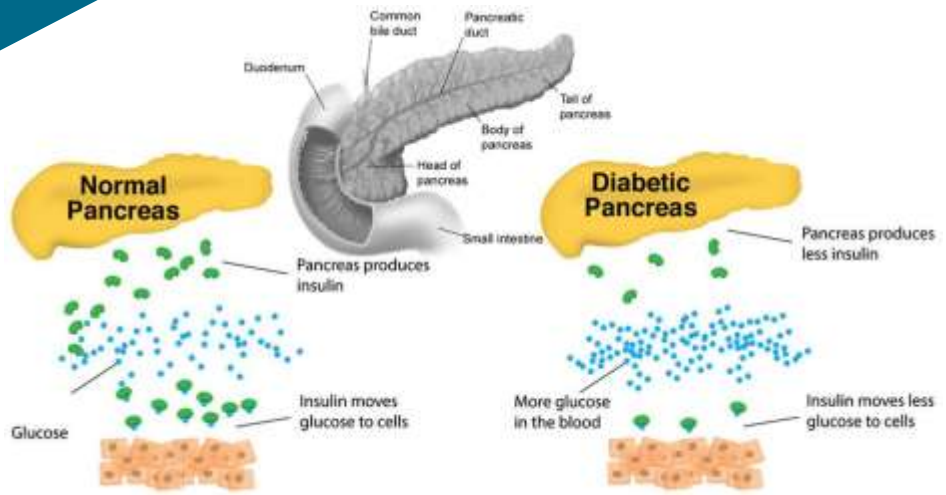
- **β - cell disfunction**

Inadequate insulin secretion and hyperglycemia

- **Insulin resistance**
- Peripheral tissues become less responsive to insulin

Usually affects **adults**; an increase in **child obesity** leads to development in children and adolescents

Type 2 Diabetes



Kumar V, Abbas AK, Aster JC. *Robbins Patologia Básica*.; 2013.

Introduction - Cr(III) and type 2 diabetes

- Cr(III) has a role in **carbohydrate and lipid metabolism**

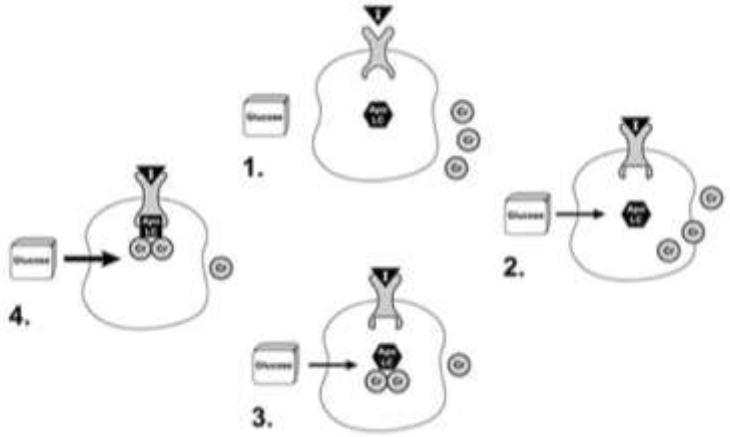
It is thought that it may have an effect on Type 2 Diabetes

Possible **reduction of insulin resistance** and reduction of hyperglycemia

Cr(III) supplements as an alternative to common medications used to improve insulin sensitivity, as these have several adverse effects.

Hua Y, Suzanne C, Jun R, Nair S. Molecular Mechanisms of Chromium in Alleviating Insulin Resistance NIH Public Access. *J Nutr Biochem*. 2013;23(4):313-319.

Potential effects of Chromium on insulin action



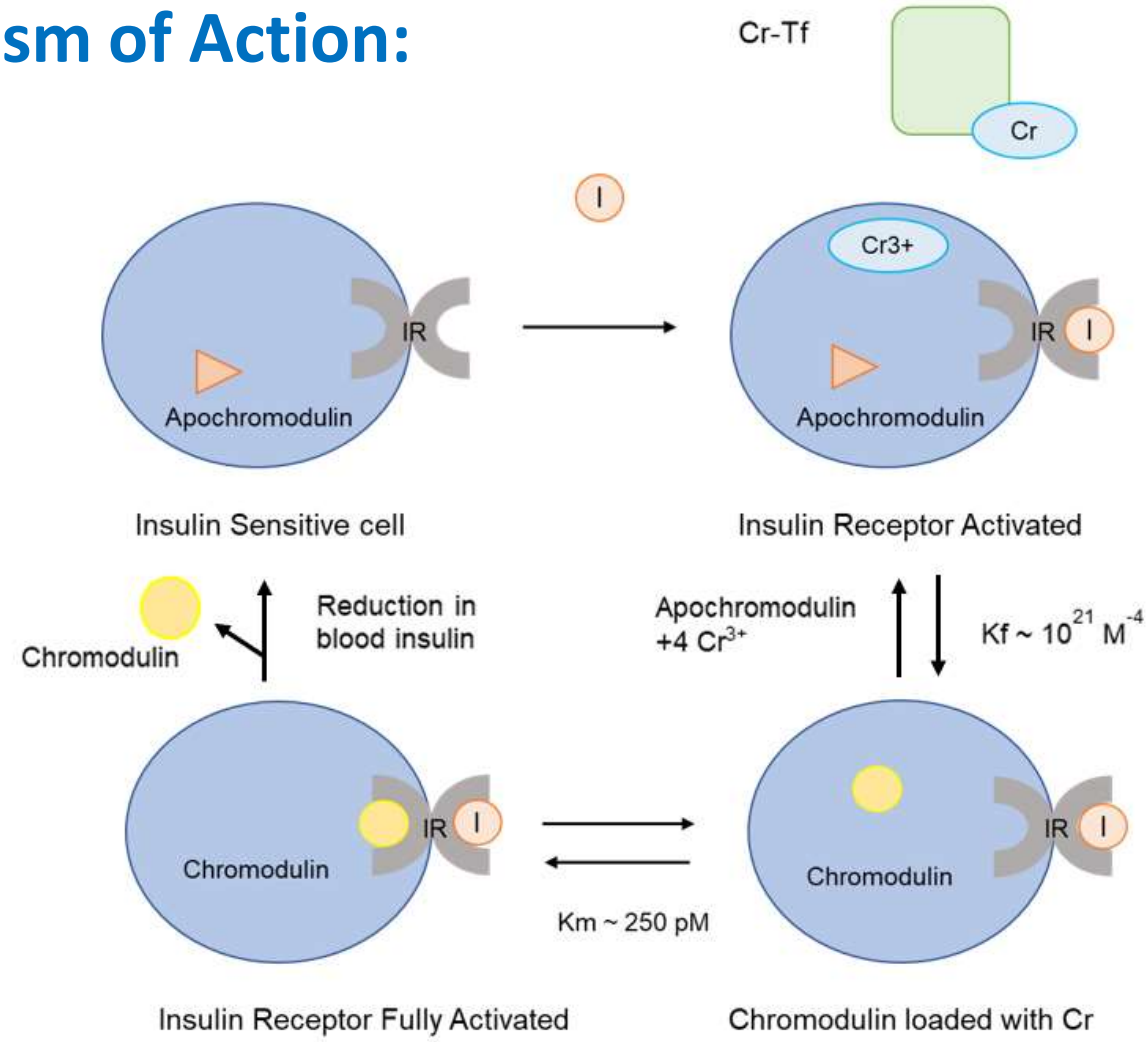
1. Insulin binds to and activates the insulin receptor.
2. Insulin receptor activation stimulates the movement of chromium into the cell.
3. Chromium binds to a peptide known as Apo-LMWCr* (Apo-LC).
4. Functional LMWCr (LC) binds to the insulin receptor and enhances its activity.

*LMWCr = low-molecular weight chromium-binding substance

Adapted from Vincent, J.B. Quest for the molecular mechanism of chromium action and its relationship to diabetes. Nutr Rev. 2000; 58: 67-72.

Introduction

Mechanism of Action:



Introduction

Is Cr(III) essential or not?

"(…) patients on TPN have developed impaired glucose tolerance and neuropathy or encephalopathy that could be reversed only by Cr infusion."

Vincent JB. Chromium: Celebrating 50 years as an essential element? *Dalt Trans*. 2010;39(16):3787-3794.

"These studies do not provide evidence for chromium being an essential element, but they may suggest that large doses of chromium may **have pharmacologic effects** in humans (…)"

"(…) nutritional studies **have failed** to provide evidence that chromium is an essential element (…)"

Vincent JB. New Evidence against Chromium as an Essential Trace Element. J Nutr. 2017;147(12):2212-2219.

Introduction

Chromium, as Cr(III) has been considered in the last 50 years an essential micronutrient, associated to lipid and carbohydrate metabolism.

- impact on reproductive hormonal axis, control on spermatogenesis,
- DNA damage,
- oxidative stress

Strong evidences confirm spermatogenesis disruption and poor semen quality.

Introduction

Nutritional Supplements with Cr(III):Tris–Picolinate Chromium(III)

Medicinal Pharmacology/
Industry of Food
Supplements

Cr(III) – classified as an **essential element** due to its (possible) important role in living systems (*Vincent, 2010*) – Regulation of carbohydrates and lipid metabolism

Diabetes *Mellitus type II*
Weight Loss/ Obesity
Muscle Gain
Cardiovascular Disorders

Vincent JB. *Dalton Transactions* 2010; 39: 3787–3794.

Supplements

Claims

Cr(III) supplements became famous in the 1990's for their claims to improve muscle development and help with weight loss.

Sales

Industries that produce them have a revenue of around $85 million per year, which accounts for almost 6% of the supplement market.

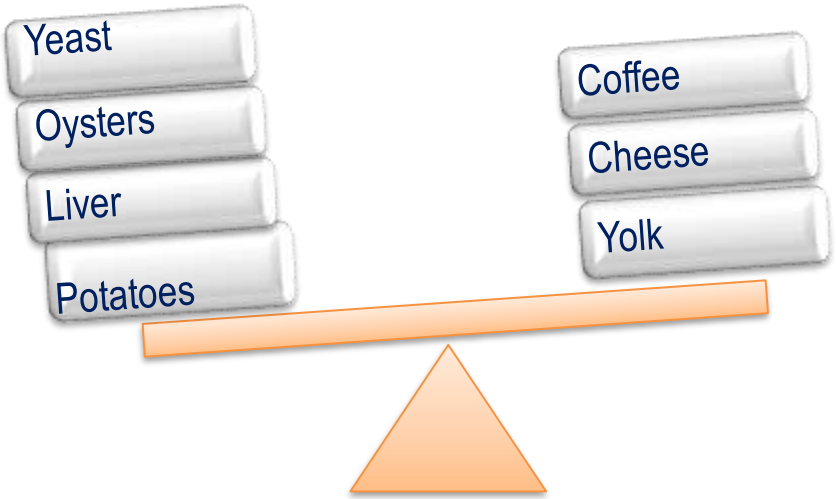
Danger

Even though studies have not shown robust results related to these claims; supplements are still commercialized, and the recommended doses are not yet known to be safe.

Merry C. Do Chromium Supplements Do Anything? We Review The Research. Healthy But Smart.com.

Introduction - Cr(III)-tris(picolinate) - dietary supplement, recommended for humans and cattle

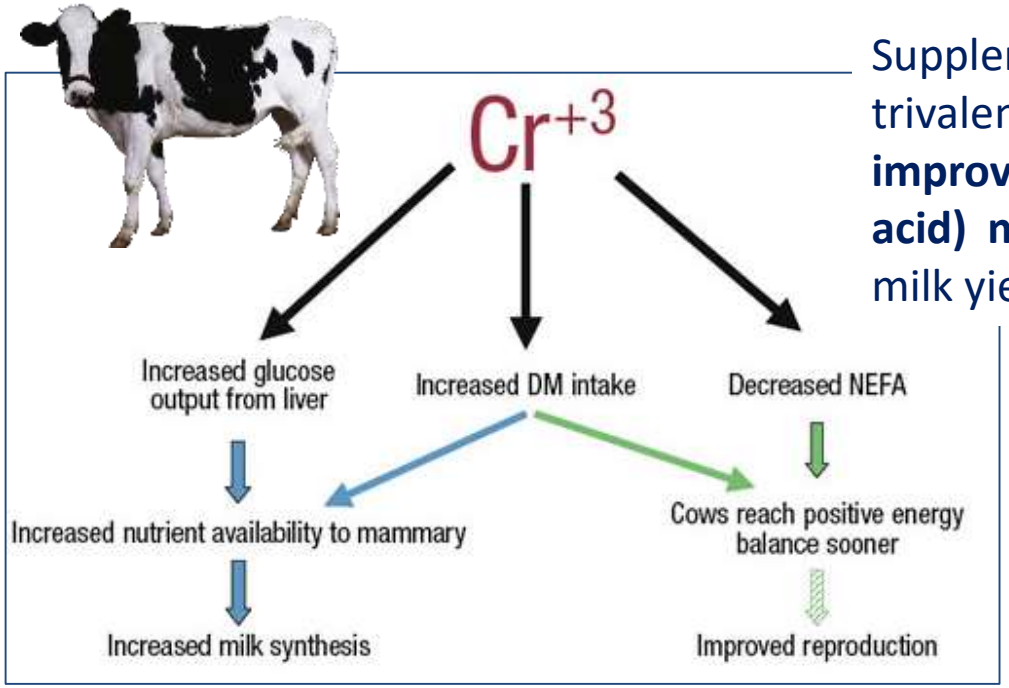
USA Academy of Sciences & National Research Council recommends:
50 – 200 µg/day
Food & Nutrition Board of the USA National Academy of Sciences recommends : 25 - 35 µg/day



Some available:
Tablets,
Sport beverages,
Gums,
provides ca 200-600 µg Cr / day,
10 – 20x the recommended values for Cr(III) intake!!!

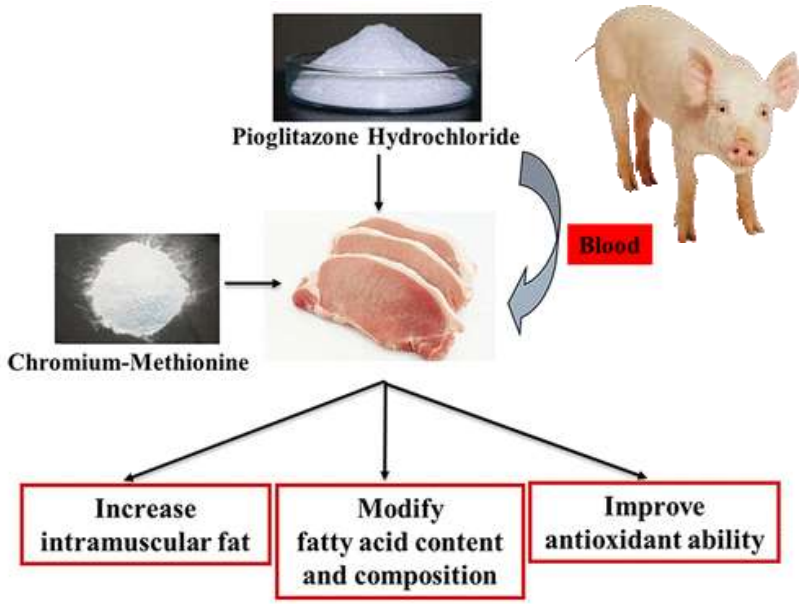
Daily intake: 10 - 40 µg
Normal plasma values: 0.1-2.1 µg/mL

Introduction - Dietary chromium supplementation recommended in cows, pigs and poultry



M. A. Soltan, 2009, J Anim Physiol a Anim Nutr 94(2):264-72.

Supplementation of dairy cattle diets with trivalent chromium has great potential to **improve glucose and NEFA (non-esterified fatty acid) metabolism**, dry matter (DM) intake and milk yields, particularly in transition cows.

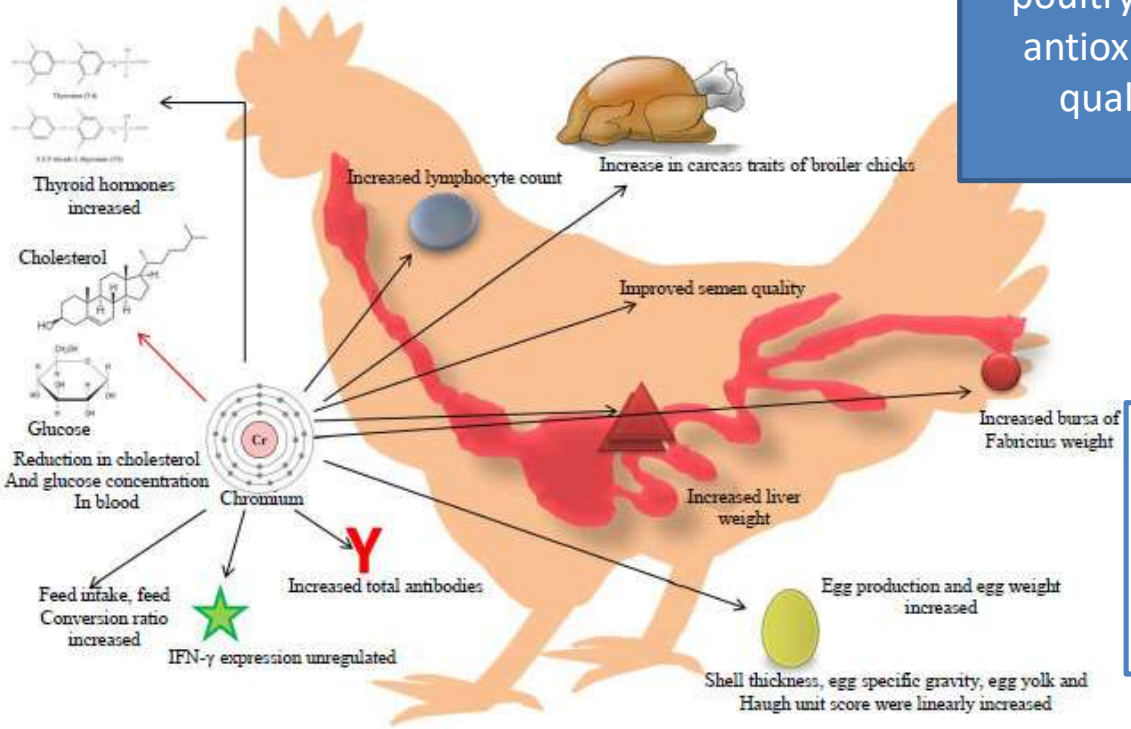


Cheng-long Jin et al., *J. Agricul. Food Chem* 2018, *66*(17), 4345-4351.

Dietary chromium supplementation already recommended in poultry nutrition

Dietary supplementation of CrPic (and nano-Cr) can improve performance and antibody titers against avian influenza and infectious bronchitis under heat stress conditions in broiler chick; improve body weight gain and feed conservation rate; Cr also linked to increased protein percentage in the meat.

Chromium importance in the poultry industry: improve antioxidant status, meat quality and immune resistance

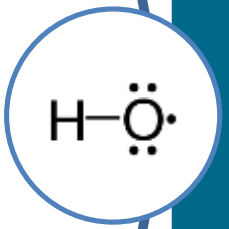


Cr ➞ stress-associated immunosuppression alleviation & enhanced immune response via interferon-gamma upregulation

Farag M. *et al.*, 2017. *Int J Pharmacol*, 13: 907-915.
Hajializadeh F. *et al*., 2017. *Vet Res forum 8*(3), 259–264.

Toxicology

Although **Cr(III)** is usually nontoxic, it can still present a threat to human health. Acute toxicity of Cr(III) can appear as teratogenic, carcinogenic, hematological toxicity, renal and liver failure.



Release of **Cr from CrPic** for use in cells requires reduction of the chromic center, which can potentially lead to production of harmful hydroxyl radicals.

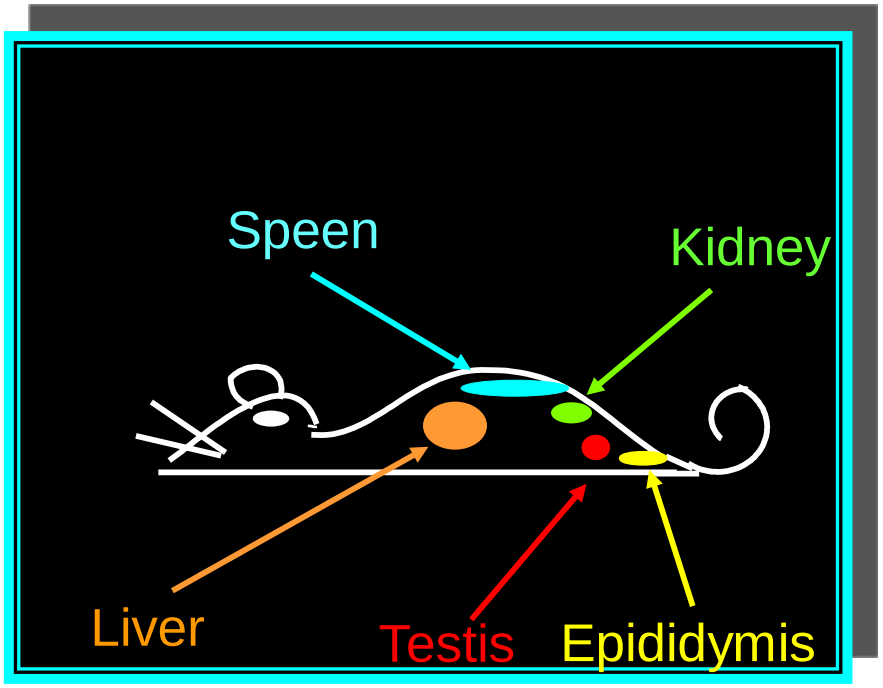
Some cases of **kidney injury** in people who took CrPic were reported; these facts raised questions on Cr(III) supplements' safety.

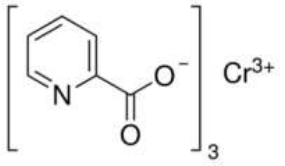
Merry C. Do Chromium Supplements Do Anything? We Review The Research. Healthy But Smart.com.

Methods

$[Cr(pic)_3]$ on mice testis and epididymis exposed to different doses

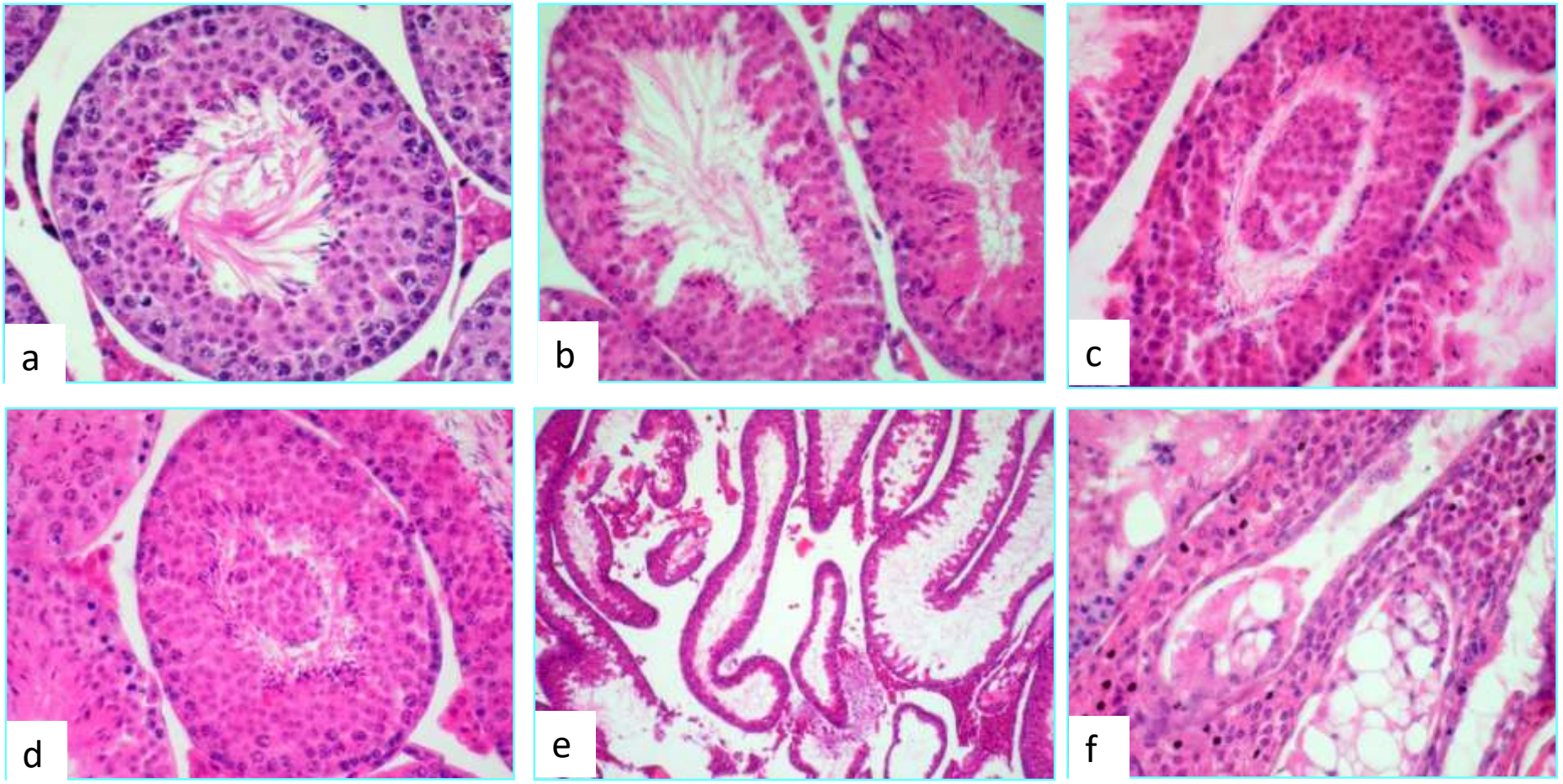
Histology investigation





25, 50 mg/kg orally for 14 days

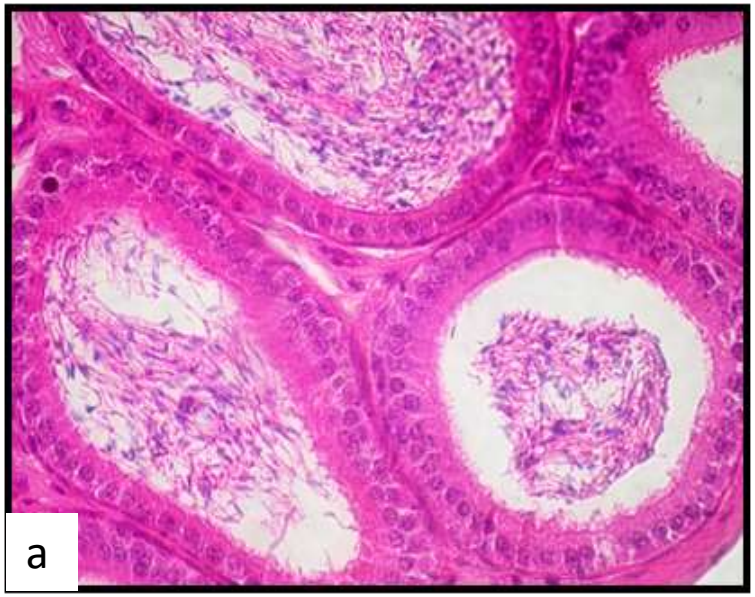
Results and discussion - $[Cr(pic)_3]$ – Testis atrophy



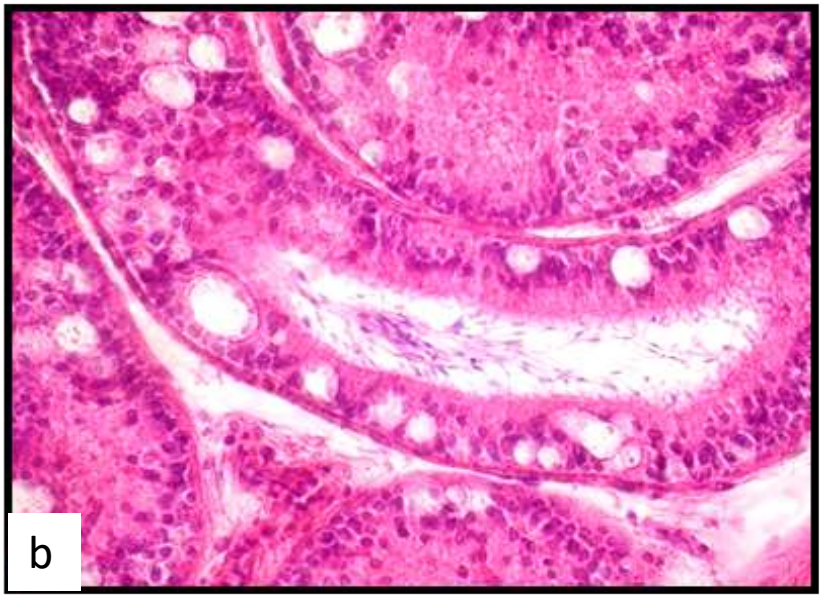
a-Control; 25 mg/kg/bw – 2 weeks (b-d); 50 mg/kg/bw $[cr(pic)_3]$- (e-f)

Ferreira *et al*., 2013 *Microscopy & Microanalysis* 19, Supplement S4, 47-48.

Results and discussion - $[Cr(pic)_3]$ – Epididymis degeneration



Control



50mg/Kg [Cr(pic)3]

- Degenerative changes
- Premature release of germ cells
- Cell depletion

Santos TM et al., Chromium: The Intriguing Element. What Biological Role Has It? (Cr(III)-Tris-Picolinate—Is It Safe or Not?). In: Thomas S, ed. *Microscopy Applied to Materials Sciences & Life Sciences.* Academic Press USA; 2018:427-459.

Conclusions of this study

- Considerable **damage on male reproductive organs** in mice in a **dose dependent manner**.

- **Concerns** on using dietary supplements based on [$Cr(pic)_3$] remain to be elucidated in future work;
- Long-term studies using several doses and perhaps higher;
- Evidence of the possible effects of [$Cr(pic)_3$], beneficial or toxic, they are not well understood and are not conclusive;
- Caution is advised in the use of [$Cr(pic)_3$], and controversy still remains.

Perspectives - Chromium supplementation and nano-applications

Harvest the benefits of a targeted therapy while avoiding possible element toxicity!

BUT

Chromium(III) oxide nanoparticles – nanodots or nanopowder - have cytotoxic potential *in vitro*!

Miyauchi A*, et al., Environ Toxicol* 2013 8(2):61-75.

HOWEVER

adverse effect on the antioxidant status

oxidative

regulate the level of hormones of carbohydrate metabolism

increasing insulin levels

reducing glucagon levels

Supplementation with Cr can increase serotonin levels and improve the antioxidant status of chickens, with no adverse effect on the secretion of other hormones

Cr (3 and 6 mg/kg) and two Cr sources: **Cr-picolinate (Cr-Pic)** and **Cr-nano (Cr-NP)**

Stępniowska A. *et al.,* Animals 2019, 24;10(1):45

Dose-dependent effects!

Perspectives - Cr supplementation and nano-applications

Main goals: improve bioavailability, protect active ingredients against degradation or reduce side effects

Jampilek J. *et al*., *Nanomaterials* 2019, *9*(2), 296.

Conclusions

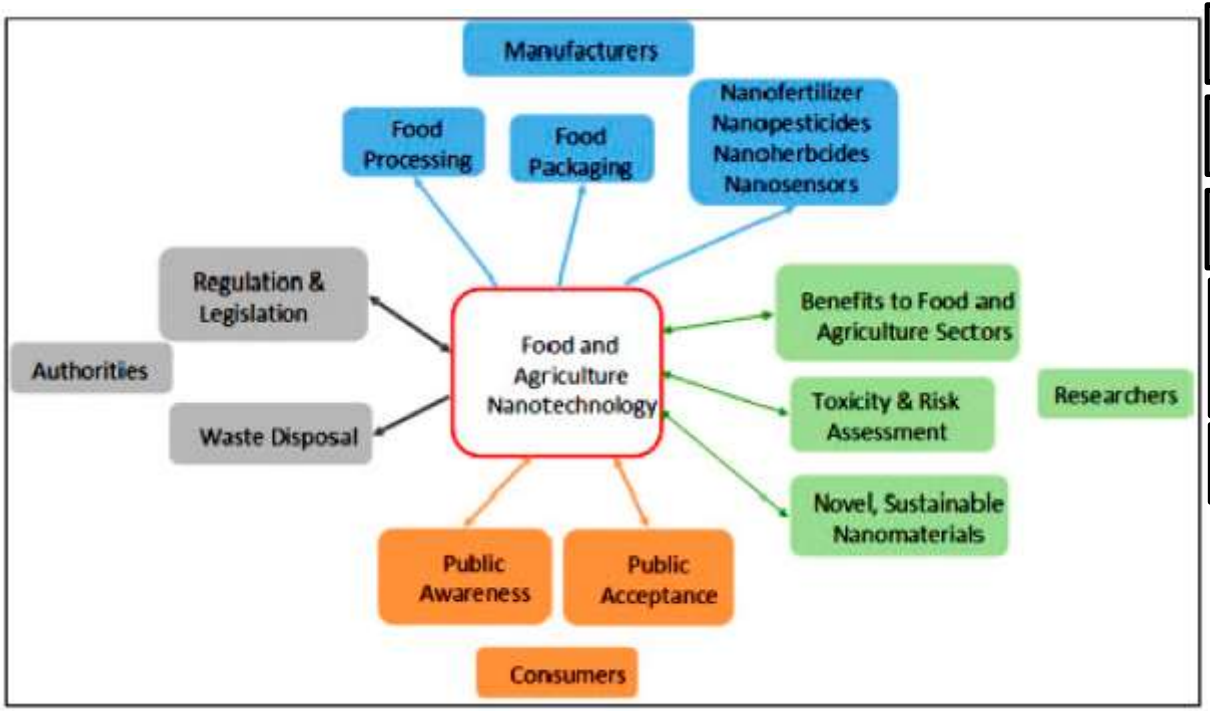
- **Chromium is vital in human and animal diets!**
- Supplementation should be assessed at individual levels!
- Fine line between beneficial and prejudicial!

Nanoapplications provide new mechanisms for targeted delivery where Cr is needed
e.g. the pancreas of diabetic patients

More comprehensive studies are needed to fully characterize chromium III mechanisms in human diet and health

Nanotechnology will be crucial for improved human and animal nutrition

New nanomaterials along with their applications are emerging within the upcoming years; Also essential is the improvement of analytical tools that will allow accurate and reliable quantification of the planned nanomaterials in a multifaceted (micro)environmental sample



- Nano-medicine
- Bio-kinetics
- Pharmacology
- Molecular biology
- Physiology

Health nutrition improved!

He X *et al. J. Food Drug Anal.* 2019, 27, 1–21
Das G. *et al.*, *Int. J. Environ. Res. Public Health* 2019, 16(23), 4848.

Acknowledgments

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