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# Safety Profile of Verdye and the myth of Iodine Allergy Concerns


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## SAFETY PROFILE – VERDYE (INDOCYANINE GREEN)

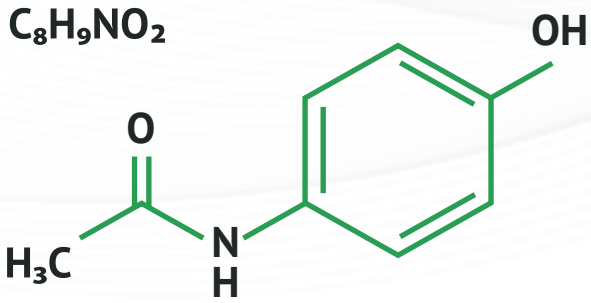
Verdye (Indocyanine Green, ICG) has a well-documented high safety and tolerability profile.[1] Combined with its unique pharmacokinetic and photo physical properties, ICG/Verdye enjoys wide acceptance and is used routinely in fluorescence guided procedures around the world.

ICG is inherently safe because it is not metabolised in the body and is excreted largely unchanged.[2] It is exclusively eliminated by the liver, excreted into the bile, with no significant renal excretion and does not cross the placental barrier.[3] ICG's specific pharmacokinetic profile, especially its exclusive hepatic clearance, makes it an inherently safe and thus extremely valuable tool for surgeons and clinicians be that for perfusion assessment, liver function evaluation, ophthalmic angiography or breast sentinel lymph node detection.


## ICG (VERDYE) IS SAFER THAN PARACETAMOL

Safety data relating to ICG shows that it has a safety profile superior to paracetamol. As part of its pharmacovigilance requirements, Diagnostic Green meticulously gathers all data concerning adverse drug reactions (ADRs) linked to ICG worldwide. Diagnostic Green has identified ADRs occurring 'very rarely' following ICG administration ('very rarely is defined as occurring less than 1 in 10,000 patients) and may include rash, urticaria and anaphylactic shock.

In contrast, a commonly prescribed medication like paracetamol (known as acetaminophen in USA) has a higher frequency of rash and urticaria (greater than 1 in 10,000 to less than 1 in 1,000).[4] This comparison underscores the significantly low occurrence of ADRs associated with ICG. Notably, both paracetamol and ICG have a comparably low frequency of anaphylactic shock in patients. Surgeons frequently highlight the exceptional safety profile of ICG in their peer-reviewed journal articles.[5]




Paracetamol Acetaminophen

## DEBUNKING THE IODINE ALLERGY MYTH


[1] *Alander, J. T., Kaartinen, I., Laakso, A., Pätilä, T., Spillmann, T., Tuchin, V. V., Venermo, M., & Välisuo, P. (2012). A review of indocyanine green fluorescent imaging in surgery. International journal of biomedical imaging, 2012, 940585.*

[2] *Patient Information Leaflet https://diagnosticgreen.com/row/product-information/*

[3] *Rubinchik-Stern, M., Shmuel, M., Bar, J., Eyal, S., & Kovo, M. (2016). Maternal-fetal transfer of indocyanine green across the perfused human placenta. Reproductive toxicology (Elmsford, N.Y.), 62, 100-105.*

[4] *Pharmacovigilance data on file by Diagnostic Green*

[5] *Pubmed https://pubmed.ncbi.nlm.nih.gov/*

Recent clinical publications demonstrate that iodine allergy is biologically impossible and is largely misunderstood.[6] Indeed Verdye's own package insert contains the following statement, "VERDYE is contraindicated for safety reasons in patients with hypersensitivity to iodine".[2] A legacy contra-indication, multiple peer-reviewed publications have proven that patients cannot be allergic to iodine. This earlier misconception arose from misinterpretation of adverse reactions to iodine-containing radiocontrast dyes and allergies to shellfish.[6]

***"THE MYTH OF IODINE'S RELATIONSHIP TO ALLERGIC REACTIONS MUST BE REFUTED TO ALLOW ICG USE IN PATIENTS WITH A HISTORY OF CONTRAST MEDIA OR SHELLFISH ALLERGY".[7]***

*Presented here are the most recent findings concerning iodine and allergies*

## A patient cannot have an iodine allergy.[8]

- Iodine plays a critical role in human physiology and is converted to iodide in the digestive process.
- The human body requires iodine to produce thyroid hormones, so an iodine allergy would be incompatible with life.[10]
- Iodine is an essential micronutrient and required by the human body throughout all stages of life, with the most critical period being from fetal development through early childhood.
- Severe iodine deficiency can cause goiter (visible thyroid swelling) and, if it occurs during pregnancy, may lead to mental retardation of the newborn.[11]
- By accepting the misconception that someone has an "iodine allergy", patients may be denied access to radiologic and fluorescence guided procedures, which could be crucial for saving their lives or significantly improving their health.

## Shellfish allergy does not equate to Iodine allergy.[9]

- Patients are often categorised as being allergic to iodine after reacting to iodine-rich compounds e.g. shellfish and fish, such as cod and tuna.
- Shellfish contain high levels of iodine, and when an incorrect link was made between iodine in radiocontrast dye and allergies, physicians likely extended this association to shellfish.[12]
- The primary allergens in shellfish are tropomyosin's, proteins crucial for muscle contraction, with no connection to iodine.[12]
- Fish allergies are usually a reaction to the muscle protein parvalbumin, so people allergic to shellfish can typically eat scaled fish including cod and tuna.
- The evidence suggests that asking if patients are allergic to shellfish, fish or iodine has no relevance to radiocontrast allergies.
- This questioning perpetuates the 'allergy' myth of an association between shellfish, iodine and contrast agents.

Some further Scientific Information on Indocyanine Green and Iodine/Sodium Iodide.

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[6] *Stewart M. W. (2022). Doctor I Have an Iodine Allergy. Ophthalmology and therapy, 11(3), 931-938.*

[7] *Capasso, I., Cucinella, G., Volcheck, G., McGree, M., Fought, A. J., Chuzhyk, O., De Vitis, L. A., Schivardi, G., Fumagalli, D., Occhiali, T., Fanfani, F., Chiantera, V., Scambia, G., Reynolds, E., Mariani, A., & Glaser, G. (2024). Let go of the myth: safety of indocyanine green for sentinel lymph node mapping in endometrial cancer. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society, 34(1), 80-87. https://doi.org/10.1136/jgc-2023-004918*

[8] *Wulf, N. R., Schmitz, J., Choi, A., & Kapusnik-Uner, J. (2021). Iodine allergy: Common misperceptions. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists, 78(9), 781-793*

[9] *What is an iodine intolerance? https://www.medicalnewstoday.com/articles/321393#symptoms*

[10] *Böhm, I., Hasembank Keller, P. S., & Heverhagen, J. T. (2016). "Iodine Allergy" - The Neverending Story. "Jodallergie" - die endlose Geschichte. RoFo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin, 188(8), 733-734.*

[11] *Delange F. (1994). The disorders induced by iodine deficiency. Thyroid : official journal of the American Thyroid Association, 4(1), 107-128.*

[12] *Schabelman, E., & Witting, M. (2010). The relationship of radiocontrast, iodine, and seafood allergies: a medical myth exposed. The Journal of emergency medicine, 39(5), 701-707.*

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## THERE IS NO 'ALLERGY TO IODINE" ISSUE WITH INDOCYANINE GREEN 8

- The ICG molecule does not contain iodide. However, due to the requirements of the production process, Verdye lyophilised powder contains the salt sodium iodide, which makes reconstituting the dye easier.
- Sodium iodide may be necessary for patients who lack sufficient iodine in their diet and is used to prevent or treat iodine deficiency.[14]
- The potential link between an iodine/iodide allergy and ICG compounds such as Verdye has been suggested, but this reaction is unlikely. Since the human body requires iodide for normal function, **an allergic reaction to sodium iodide, as found in the Verdye product, is not possible.**[15]
- In a recent study of patients including those with documented iodine or contrast allergy, no ICG anaphylactic reactions occurred.[16]

**Please Note:** A diagnostic application of Indocyanine Green means a total dose of up to 840 µg of iodide can be administered. This may pose a risk for patients suffering from hyperthyroidism. In these patients Verdye should only be used with caution or not administered at all.

For full product information go to the summary of product characteristics (SmPC) document for your specific territory.

### HOW ALLERGIES OCCUR

- "Allergy is an abnormal or exaggerated reaction to exogenous stimuli which involves various types of hypersensitivity reactions engaging antibodies, immune cell-mediated, tissue-driven or metabolic mechanisms resulting in the development of respiratory, skin, eye, gastrointestinal and other symptoms, including anaphylaxis."[17]
- Some drugs can trigger anaphylaxis by directly activating immune cells, even without antibodies being involved. These include heparin, aspirin, other NSAIDs, certain antibiotics like vancomycin, fluoroquinolones, opioids, and anesthesia drugs, especially muscle relaxants.[18]

### IODINATED DRUGS

- Reactions to iodine-containing disinfectants, such as Povidone Iodine are often labeled as 'iodine allergy'. However, this is inaccurate, as these reactions are likely due to other substances in these products, as is the case for Povidone, rather than the iodine itself.[8,19]
- Reactions to iodinated contrast media are likely caused by high osmolarity or ionic content of the dye.[8,19]

[13] *Prof. Dr. Med. R. Hehrmann, Department of Endocrinology, Medical Director, Diakonie Krankenhaus, Stuttgart, Germany*

[14] *Bath, S. C., Verkaik-Kloosterman, J., Sabatier, M., Ter Borg, S., Eilander, A., Hora, K., Aksoy, B., Hristozova, N., van Lieshout, L., Taniu Besler, H., & Lazarus, J. H. (2022). A systematic review of iodine intake in children, adults, and pregnant women in Europe-comparison against dietary recommendations and evaluation of dietary iodine sources. Nutrition reviews, 80(11), 2154-2177.*

[15] *Wulf, N. R., Schmitz, J., Choi, A., & Kapusnik-Uner, J. (2021). Iodine allergy: Common misperceptions. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists, 78(9), 781-793.*

[16] *Zammarrelli, W. A., 3rd, Afonso, A. M., Broach, V., Sonoda, Y., Zivanovic, O., Mueller, J.J., Leitao, M. M., Jr, Chan, A., & Abu-Rustum, N. R. (2021). Sentinel lymph node biopsy in patients with endometrial cancer and an indocyanine green or iodinated contrast reaction - A proposed management algorithm. Gynecologic oncology, 162(2), 262-267.*

[17] *Jutel, M., Agache, I., Zemelka-Wiacek, M., Akdis, M., Chivato, T., Del Giacco, S., Gajdanowicz, P., Gracia, I. E., Klimek, L., Lauerma, A., Ollert, M., O'Mahony, L., Schwarze, J., Shamji, M. H., Skypala, I., Palomares, O., Pfaar, O., Torres, M. J., Bernstein, J. A., Cruz, A. A., ... Akdis, C. A. (2023). Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy, 78(11), 2851-2874.*

[18] *Cianferoni A. (2021). Non-IgE-mediated anaphylaxis. The Journal of allergy and clinical immunology, 147(4), 1123-1131.*

[19] *Brouse, S. D., & Phillips, S. M. (2005). Amiodarone use in patients with documented allergy to iodine-containing compounds. Pharmacotherapy, 25(3), 429-434.*