

# References - Statement on the effects of excess Vitamin A on maternal health

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## References

Allen LH, Haskell M. Estimating the Potential for Vitamin A Toxicity in Women and Young Children. *Journal of Nutrition*. 2002; **132**: 2907S-2919S,.

Azaïs-Braesco V, Pascal G. Vitamin A in pregnancy: requirements and safety limits The American Journal of Clinical Nutrition, 2000, **71**(5): 1325S–1333S. [Vitamin A in pregnancy: requirements and safety limits | The American Journal of Clinical Nutrition | Oxford Academic \(oup.com\)](#)

Bagatin E, Costa CS. The use of isotretinoin for acne – an update on optimal dosing, surveillance, and adverse effects Expert Review of Clinical Pharmacology 2020, 13(8) 885–897. <https://doi.org/10.1080/17512433.2020.1796637>

Bakker MF, Peeters PHM, Klaasen VM, et al. Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort. American Journal of Clinical Nutrition 2016;**103**:454–64.

Barnard JH, Collings JC[, Whiting, A, Przyborski SA, Marder TB. Synthetic Retinoids: Structure–Activity Relationships. Chemistry: a European. Journal. 2009, 15, 11430 – 11442.

Biesalski HK. Comparative assessment of the toxicology of vitamin A and retinoids in man. Toxicology 1989;**57**:117–61.

Blaser, B., Gonit, M., Qi, H. et al. Induction of folate receptor type  $\beta$  in a bone marrow engraftment model of acute myelogenous leukemia. Leukemia **21**, 2233–2235 (2007). [Induction of folate receptor type  \$\beta\$  in a bone marrow engraftment model of acute myelogenous leukemia | Leukemia \(nature.com\)](#)

Botto LD, Khoury MJ, Miulinare J, Erickson JD. Periconceptional multivitamin use and the occurrence of conotruncal heart defects: results from a population-based, case-control study. Pediatrics 1996;**98**:911–7.

Bowman WC, Rand MJ Textbook of Pharmacology, second edition, 1982. Blackwell Scientific Publications, Oxford. ISBN 0-632 09990 9.

Brazzell RK, Colburn WA. Pharmacokinetics of the retinoids isotretinoin and etretinate: A comparative review Journal of the American Academy of Dermatology 1982 6,(4), Part 2, 643-651. [https://doi.org/10.1016/S0190-9622\(82\)70053-2](https://doi.org/10.1016/S0190-9622(82)70053-2)Get rights and content

Buss NE, Tembe EA, Prendergast BD, Renwick AG, George CF. The teratogenic metabolites of vitamin A in women following supplements and liver Human and Experimental Toxicology 1994 **13**(1):33-43. <https://doi.org/10.1177/096032719401300106>

Carta G, Murru E, Cordeddu L , Ortiz B , Giordano E, Belury MA, Quadro L, Banni S. Metabolic Interactions between Vitamin A and Conjugated Linoleic Acid Nutrients 2014, 6, 1262-1272; doi:10.3390/nu6031262 nutrients ISSN 2072-6643.

[www.mdpi.com/journal/nutrients](http://www.mdpi.com/journal/nutrients).

Choi EJ, Kim N, Kwak H-S, Han HJ, Chun KC, Kim Y-A, Koh JW, Han JY, Joo SH, Lee JS, Koren G. The rates of major malformations after gestational exposure to isotretinoin: a systematic review and meta-analysis. *Obstetrics and Gynecological Sciences* 2021;**64**(4):364-373. <https://doi.org/10.5468/ogs.20373>

Christian P, West KP Jr. Interactions between zinc and vitamin A: an update. *American Journal of Clinical Nutrition* 1998,**68**(suppl):435S-41S.

Clagett-Dame M, Knutson D. Vitamin A in Reproduction and Development. *Nutrients* 2011, **3**, 385-428; <https://doi.org/10.3390/nu3040385>.

Cohen JM, Beddaoui M, Kramer MS, Platt RW, Basso O, Kahn SR Maternal Antioxidant Levels in Pregnancy and Risk of Preeclampsia and Small for Gestational Age Birth: A Systematic Review and Meta-Analysis. *PLoS ONE* 2015 **10** (8): e0135192. <https://doi.org/10.1371/journal.pone.0135192>.

Collins MD, Mao GE. Teratology of retinoids. *Annual Review of. Pharmacology and Toxicology* 1999. **39**, 399-430.

COT (2021). [TOX-2021-44 Vitamin A in the maternal diet \(food.gov.uk\)](https://www.food.gov.uk/news/news-detail/1022)

Cox SE, Arthur P, Kirkwood BR, Yeboah-Antwi K, Riley EM. Vitamin A supplementation increases ratios of proinflammatory to anti-inflammatory cytokine responses in pregnancy and lactation. *Clinical and Experimental Immunology*, 2006 **144**: 392-400.

Cruess RL, Clark I. Alterations in the lipids of bone caused by hypervitaminosis A and D. *Biochemical Journal* 1965 **96**(1):262-265.

Czeizel AE, Rockenbauer M. Prevention of congenital abnormalities by vitamin A. *International Journal of Vitamin and Nutrient Research* 1998 **68**:219-231.

Danby FW. Retinoic acid in acne therapy. *Canadian Medical Association Journal* 1978 **119** 854.

Das BC, Thapaa P, Karkia R, Dasa S, Mahapatraa S, Liuc T-C , Torregrozac I, Wallaced DP, Kambhampatia S, Van Veldhuizenena P, Vermae A, Rayf SK, Evans T. Retinoic Acid Signaling Pathways in Development and Diseases. *Bioorganic*

Medicinal Chemistry. 2014: **22**(2): 673–683.

<https://doi.org/10.1016/j.bmc.2013.11.025>.

Dudas I, Czeizel AE. Use of 6,000 IU vitamin A during early pregnancy without teratogenic effect. *Teratology* 1992 **45**:335–336.

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2006 Tolerable upper intake levels of vitamins and minerals. ISBN: 92-9199-014-0.

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015. Scientific opinion on dietary reference values for vitamin A. *EFSA Journal* 2015;13(3):4028, 84 pp. [Scientific Opinion on Dietary Reference Values for vitamin A - - 2015 - EFSA Journal - Wiley Online Library](#)

EVM (2002) Expert Group on Vitamins and Minerals. Review of Vitamin A). [\[ARCHIVED CONTENT\] \(nationalarchives.gov.uk\)](#)

EVM (2003) Expert Group on Vitamins and Minerals. Safe Upper Levels for Vitamins and Minerals. [vitmin2003.pdf \(food.gov.uk\)](#)

FAO/WHO (1975) Revision of the Directive on colouring matters authorized for use in foodstuffs intended for human consumption Reports of the Scientific Committee for Food. First Series p17 – 30.

FAO/WHO (1974) Eighteenth Report of the Joint FAO/WHO Expert Committee on Food Additives, Wld Hlth Org. techn. Rep. Ser., 1974, No. 557.FAO Nutrition Meetings Report Series, 1974, No. 54.

FAO/WHO (2019) Eighty- seventh meeting Rome, 4–13 June 2019. [ca5270en.pdf \(fao.org\)](#)

Goodman GE, Alberts DS, Peng YM, Beaudry J, Leigh SA, Moon TE Plasma kinetics of oral retinol in cancer patients *Cancer Treatment Reports* 1984 **68** (9):1125-1133.

Goodman GE, Thornquist MD, Balmes J, Cullen MR, Meyskens FL Jr., Omenn GS, Valanis B, Williams JH Jr. The beta-carotene and retinol efficacy trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping b-carotene and retinol supplements. *Journal of the National Cancer Institute* 2004;**96**:1743–1750.

Greenberg R, Cornbleet T, Joffay A I. (1959) Accumulating and excretion of vitamin a-like fluorescent material by sebaceous glands after the oral feeding of

various carotenoids. *Journal of Investigational Dermatol.*, **32**, 599.

Händel, MN, Moon RJ, Titcombe P, Abrahamsen B, Heitmann BL, Calder PC, Dennison EM, Robinson SM, Godfrey KM, [Inskip](#) HM, Cooper C, Harvey NC. Maternal serum retinol and  $\beta$ -carotene concentrations and neonatal bone mineralization: results from the Southampton Women's Survey cohort. *American Journal of Clinical Nutrition*. 2016 **104**(4): 1183-1188.

Harika R, Faber M, Samuel F, Kimiywe J, Mulugeta A, Eilander A micronutrient status and dietary intake of iron, vitamin A, iodine, folate and zinc in women of reproductive age and pregnant women in Ethiopia, Kenya, Nigeria and South Africa: a systematic review of data from 2005 to 2015. *Nutrients* 2017, **9**: 1096; <https://doi.org/10.3390/nu9101096>.

Hartmann S, Brørs O, Bock J, Blomhoff R, Bausch J, Wiegand U-W, Hartmann D, Hornig DH. Exposure to retinyl esters, retinol, and retinoic acids in non-pregnant women following increasing single and repeated oral doses of vitamin A *Annals of Nutrition and Metabolism*. 2005; **49**(3):155-64 <https://doi.org/10.1159/000086879>.

Howard WB, Willhite CC: Toxicity of retinoids in humans and animals. *Journal of Toxicology Toxin Reviews* 1986; **5**:55-94.

Huang P, Chandra V, Rastinejad F. Retinoic Acid Actions Through Mammalian Nuclear Receptors. *Chemical Reviews* 2014 **114**(1): 233-254. <https://doi.org/10.1021/cr400161b>.

Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC): [National Academies Press \(US\)](#); 2001.

Jenab M, Salvini S, van Gils CH, Brustad M, Shakya-Shrestha S, Buijsse B, Verhagen H, Touvier M, Biessy C, Wallström P, Bouckaert K, Lund E, Waaseth M, Roswall N, Joensen AM, Linseisen J, Boeing H, Vasilopoulou E, Dilis V, Sieri S, Sacerdote C, Ferrari P, Manjer J, Nilsson S, Welch AA, Travis R, Boutron-Ruault MC, Niravong M, Bueno-de-Mesquita HB, van der Schouw YT, TormoMJ, Barricarte A, Riboli E, Bingham S, Slimani N. Dietary intakes of retinol,  $\beta$ -carotene, vitamin D and vitamin E in the European Prospective Investigation into Cancer and Nutrition cohort. *European Journal of Clinical Nutrition* 2009 **63**, S150-S178.

Kamm JJ, Toxicology, carcinogenicity, teratogenicity of some orally administered retinoids. *Journal of the American Academy of Dermatology* 1982;6(4), Part 2, 652-659.

Khoury MJ, Moore CA, Mulinare J. Vitamin A and birth defects. *Lancet* 1996 **347**:322.

Kizer KW, Fan AM, Bankowska J, Jackson RJ, Lyman DO. Vitamin A- a pregnancy hazard alert. *Western Journal of Medicine* 1990; **152**:78-81).

Kriangkrai R, Chareonvit S, Iseki S, Limwongse V. Pretreatment Effect of Folic Acid on 13-Cis-RA-Induced Cellular Damage of Developing Midfacial Processes in Cultured Rat Embryos *Open Dent J.* 2017; **11**: 200–212.

Kwak-Kim JY, Chung-Bang HS, Ng SC, Ntrivalas EI, Mangubat CP, Beaman KD, Beer AE, Gilman-Scachs A., et al. Increased T helper 1 cytokine responses by circulating T cells are present in women with recurrent pregnancy losses and in infertile women with multiple implantation failures after IVF. *Human Reproduction* 2003; **18**:767–773.

Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JY, Curry CJ, Fernhoff PM, Grix Jr AW, Lott IT, et al. Retinoic acid embryopathy *New England Journal of Medicine* 1985 **313**(14):837-41. <https://doi.org/10.1056/nejm198510033131401>.

Lammer EJ: Embryopathy in infant conceived one year after termination of maternal etretinate (Letter). *Lancet* 1988; **2**:1080-1081.

Latriano L, Tzimas G, Wong F, Wills RJ The percutaneous absorption of topically applied tretinoin and its effect on endogenous concentrations of tretinoin and its metabolites after single doses or long-term use *Journal of the American Academy of Dermatology* 1997 **36**(3 Pt 2):S37-46.

Lee LMY, Leunga C-Y, Tanga WWC, Choia HL, Leung YC, McCaffery PJ, Wanga C-C, Woolfe AS, Shuma ASW. A paradoxical teratogenic mechanism for retinoic acid. *PNAS* 2012 **109**(3), 13668–13673.

Li C, Chen J, Wang W, Ai M, Zhang Q, Kuang L. Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis *BMJ Open.* 2019; **9**(1): e021549. doi: [10.1136/bmjopen-2018-021549](https://doi.org/10.1136/bmjopen-2018-021549) .

Loughrill E, Govinden P, Zand N. Vitamins A and E content of commercial infant foods in the UK: A cause for concern? *Food Chemistry* 2016 **210**:56-62. <https://doi.org/10.1016/j.foodchem.2016.04.014>.

Luvizotto PP, Schmitt JV Depressive symptoms before and during treatment of acne with isotretinoin and its correlations: a prospective study *Anais Brasileiros Dermatologias*. 2020 95(6): 760–763.

Lynn RC, Poussin M, Kalota A, Feng Y, Low PS, Dimitrov DS, Powell DJ Jr. Targeting of folate receptor  $\beta$  on acute myeloid leukemia blasts with chimeric antigen receptor-expressing T cells *Blood* 2015 **125**(22): 3466–3476.

MacDonald SC, Cohen JM, Panchaud A, McElrath TF, Huybrechts KF, Hernández-Díaz S. Identifying Pregnancies in Insurance Claims Data: Methods and Application to Retinoid Teratogenic Surveillance. *Pharmacoepidemiological Drug Safety*. 2019 **28**(9): 1211–1221. <https://doi.org/10.1002/pds.4794>.

Maden M. Vitamin A and the developing embryo. *Postgraduate Medical Journal* 2001;**77**:489-491.

Magin P, Pond D, Smith W. Isotretinoin, depression and suicide: a review of the evidence *British Journal of General Practice* 2005 **55**(511): 134–138.

Marshall H, Nonchev S, Sham MH, Muchamore I, Lumsden A, Krumlauf R. [Retinoic acid alters hindbrain Hox code and induces transformation of rhombomeres 2/3 into a 4/5 identity](#). *Nature*. 1992 **360**(6406):737-41. doi: 10.1038/360737a0.

Martines-Frias ML, Salvador J. Epidemiological aspects of prenatal exposure to high doses of vitamin A in Spain. *European Journal of Epidemiology* 1990;**6**:118–23.

Mawson AR, Croft AM. Rubella Virus Infection, the Congenital Rubella Syndrome, and the Link to Autism. *International Journal of Environmental Research and Public Health* 2019, **16**: 3543; <https://doi.org/10.3390/ijerph16193543>.

Merck Index, 12<sup>th</sup> edition Merck & Co. Inc. Whitehouse Station NJ 1996 ISBN 0911910-12-3.

Metz AL, Walser MM, Olsen WG. The interaction of dietary vitamin A and vitamin D related to skeletal development in the turkey poult. *Journal of Nutrition* 1985 **115**: 929-935.

Mills JL, Simpson JL, Cunningham GC, Conley MR, Rhoads GG. Vitamin A and birth defects. *American Journal of Obstetrics and Gynecology* 1997;**177**:31– 36.

Nagel G, Linseisen J, van Gils CH et al. Dietary  $\beta$ -carotene, vitamin C and E intake and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Breast Cancer Research and Treatment* 2010 **119**, 753–765  
<https://doi.org/10.1007/s10549-009-0444-8>.

(NTP (2012) National Toxicology Program. NTP technical report on the photo-cocarcinogenesis study of retinoic acid and retinyl PALMITATE [NTP technical report on the photo-cocarcinogenesis study of retinoic acid and retinyl PALMITATE](#)

Nau H. Chemical structure - teratogenicity relationships, toxicokinetics and metabolism in risk assessment of retinoids. *Toxicology Letters* 1995 ;**82/83** : 975-979.

NHS advice on vitamins and minerals: Vitamin A. Last reviewed, August 2021. Vitamins and minerals - Vitamin A - NHS ([www.nhs.uk](http://www.nhs.uk))

NHS Foods to avoid during pregnancy. Last reviewed August 2021. Foods to avoid in pregnancy - NHS ([www.nhs.uk](http://www.nhs.uk))

Nohynek GJ, Meuling WJA, Vaes WHJ, Lawrence RS, Shapiro S, Schulte S, Steiling W, Bausch J, Gerber E, Sasa H, Nau H. Repeated topical treatment, in contrast to single oral doses, with Vitamin A-containing preparations does not affect plasma concentrations of retinol, retinyl esters or retinoic acids in female subjects of child-bearing age *Toxicology Letters* 2006;**163**(1):65-76  
<https://doi.org/10.1016/j.toxlet.2005.09.029>.

Omenn GS, Goodman G, Thornquist M, Grizzle J, Rosenstock L, Barnhart S, Balmes J, Cherniack MG, Cullen MR, Glass A, Keogh J, Meyskens FJr, Valanis B, Williams J Jr. The  $\beta$ -Carotene and Retinol Efficacy Trial (CARET) for Chemoprevention of Lung Cancer in High Risk Populations: Smokers and Asbestos-exposed Workers. *Cancer Research Suppl* 54. 2(B8s-2II43s, April 1. IW4)

O'Reilly KC, Shumake J, Gonzalez-Lima F, Lane, MA, Bailey SJ. Chronic Administration of 13-Cis-Retinoic Acid Increases Depression-Related Behavior in Mice *Neuropsychopharmacology* (2006) 31, 1919–1927  
<https://doi.org/10.1038/sj.npp.1300998>.

Ortega-Senovilla H, Alvino G, Taricco E, Cetin I, Herrera E. Enhanced circulating retinol and non-esterified fatty acids in pregnancies complicated with intrauterine growth restriction. *Clin Sci*. 2010; **118**(5):351–8.



Ozaki R, Kuroda K, Ikemoto Y, Ochiai A, Matsumoto A, Kumakiri J, et al. Reprogramming of the retinoic acid pathway in decidualizing human endometrial stromal cells. PLoS ONE 2017; **12**(3): e0173035  
<https://doi.org/10.1371/journal.pone.0173035>.

Panchaud A, Csajka C, Merlob P, Schaefer C, Berlin M, De Santis M, Vial T, Ieri A, Malm H, Eleftheriou G, MD, PhD, MSc, Bracha Stahl, MPharm, Philippe Rousso, MD, Ursula Winterfeld, Rothuizen LE, Buclin T, Pregnancy outcome following exposure to topical retinoids: A multicenter prospective study Journal of Clinical Pharmacology, 2012 **52**:1844-1851.

Parr CL, Magnus MC, Karlstad Ø, Holvik K, Lund-Blix NA, Haugen M, Page CM, Nafstad P, Ueland PM, London SJ, Håberg SE, Nystad W. Vitamin A and D intake in pregnancy, infant supplementation, and asthma development: the Norwegian Mother and Child Cohort. American Journal of Clinical Nutrition 2018;**107**:789-798.

[Piersma AH](#), [Bode W](#), [Verhoef A](#), [Olling M](#). Teratogenicity of a Single Oral Dose of Retinyl Palmitate in the Rat, and the Role of Dietary Vitamin A Status [Pharmacology & Toxicology](#) 1996 79(3): 131-135.

Piersma AH, Hessel EV, Staal YC. Retinoic acid in developmental toxicology: Teratogen, morphogen and biomarker [Reproductive Toxicology](#) 2017 **72**: 53-61.

Qi H, Ratnam M. Synergistic induction of folate receptor beta by all-trans retinoic acid and histone deacetylase inhibitors in acute myelogenous leukemia cells: mechanism and utility in enhancing selective growth inhibition by antifolates Cancer Research 2006 **66**(11):5875-5882. [Synergistic induction of folate receptor beta by all-trans retinoic acid and histone deacetylase inhibitors in acute myelogenous leukemia cells: mechanism and utility in enhancing selective growth inhibition by antifolates. - Abstract - Europe PMC](#)

Penniston KL, Tanumihardjo SA The acute and chronic toxic effects of vitamin A. American Journal of Clinical Nutrition 2006;**83**:191-201.

Raghupathy R, Makhseed M, Azizieh F, Hassan N, Al-Azemi M, Al-Shamali E. Maternal Th1- and Th2-Type Reactivity to Placental Antigens in Normal Human Pregnancy and Unexplained Recurrent Spontaneous Abortions Cellular Immunology 1999 **196**:122-130.

Raghupathy R, Makhseed M, Azizieh F, Omu A, Gupta M, Farhat R. Cytokine production by maternal lymphocytes during normal human pregnancy and in

unexplained recurrent spontaneous abortion. Human Reproduction 2000; **15**:713-718.

Ritchie HE, Webster WS, Eckhoff C, Oakes DJ. Model predicting the teratogenic potential of retinyl palmitate, using a combined in vivo/in vitro approach. Teratology 1998 **58**: 113-123.

Robson J, Moss N, McGettigan P, Beardsley SJ, Lovegrove E, Dezateux C. First do no harm: valproate and medicines safety in pregnancy British Journal of General Practice 2020; **70** (699): 477-478.

Rohde CM, Manatt M, Clagett-Dame M, DeLuca H-F. Vitamin A antagonizes the action of vitamin D in rats. Journal of Nutrition 1999 **129**: 2246-2250,

Rosa FW: Teratogenicity of isotretinoin (Letter). Lancet 1983; **2**:513.

Rothman KJ, Moore LL, Singer MR, Nguyen U-SDT, Mannino S, Milunsky A Teratogenicity of high vitamin a intake. New England Journal of Medicine 1995; **333**:1369-73.

Russell RM The vitamin A spectrum from deficiency to toxicity American Journal of Clinical Nutrition 2000;**71**:878-84.

Rutkowski M, and Grzegorzcyk K adverse effects of antioxidative vitamins International Journal of Occupational Medicine and Environmental Health 2012;**25** (2):105 - 121. [Adverse effects of antioxidative vitamins | SpringerLink](#)

Salganik RI The benefits and hazards of antioxidants: controlling apoptosis and other protective mechanisms in cancer patients and the human population Journal of the American College of Nutrition. 2001;**20**(5 Suppl):464S-472S.

SCF (Scientific Committee on Food), 2002. Opinion on the Tolerable Upper Intake Level of preformed vitamin A (retinol and retinyl esters). [complet\\_chapitres.indd \(europa.eu\)](#)

Schnorr CE, Da Silva Morrone M, Weber MH, Lorenzi R, Behr GA, Claudio J, Moreira F. The effects of vitamin A supplementation to rats during gestation and lactation upon redox parameters: Increased oxidative stress and redox modulation in mothers and their offspring. Food and Chemical Toxicology 2011; **49**: 2645-2654.

Söderlund MB, Fex GA, Nilsson-Ehle P. Concentrations of retinoids in early pregnancy and in newborns and their mothers. American Journal of Clinical

Nutrition 2005;**81**:633– 636.

Shaw GM, Wasserman CR, Block G, Lammer EJ. High maternal vitamin A intake and risk of anomalies of structures with a cranial neural crest cell contribution. Lancet 1996 **347**:899–900.

Spiegler E, Kim Y-K, Wassef L, Shete V, Quadro L. Maternal-fetal transfer and metabolism of vitamin A and its precursor  $\beta$ -carotene in the developing tissues Biochimica et Biophysica Acta. 2012; **1821**(1): 88–98.

[Stratford T](#), [Logan C](#), [Zile M](#), [Maden M](#). Abnormal anteroposterior and dorsoventral patterning of the limb bud in the absence of retinoids. Mechanisms of Development 1999 **81**(1-2):115-25.

[Tamura K](#), [Yokouchi Y](#), [Kuroiwa A](#), [Ide H](#). Retinoic acid changes the proximodistal developmental competence and affinity of distal cells in the developing chick limb bud. Developmental Biology 1997 **188**(2):224-234Tayyem RF, Mahmoud RI, Shareef MH, Marei LS. Nutrient intake patterns and breast cancer risk among Jordanian women: a case-control study. Epidemiology and Health Volume: **41** ,.Article ID: e2019010, 7 pages. <https://doi.org/10.4178/epih.e2019010>

Van den Berg H, Hulshof KF, Deslypere JP. Evaluation of the effect of the use of vitamin supplements on vitamin A intake among (potentially) pregnant women in relation to the consumption of liver and liver products European Journal of Obstetrics, Gynecology and Reproductive Biology 1996 **66**(1):17-21.

Werler MW, Lammer EJ, Rosenberg L, Mitchell AA Maternal vitamin A supplementation in relation to selected birth defects Teratology 1990 Nov;**42**(5):497- 503. <https://doi.org/10.1002/tera.1420420506>

Wiegand UW, Hartmann S, Hummler H. Safety of vitamin A: recent results. International Journal of Vitamin Nutrition Research 1998 **68**: 411-416.

Wilkinson RD. Safety of retinoic acid in acne therapy. Canadian Medical Association Journal 1975 **113** 606.

Willhite CC, Hill RM, Irving DW, Isotretinoin-induced craniofacial malformations in humans and hamsters. J Craniofacial Genetics and Developmental Biology 1986;**2** (suppl): 193-209.

Willhite CC, Sharma RP, Allen PV, Berry DL. Percutaneous retinoid absorption and embryotoxicity. Journal of Investigational Dermatology. 1990; **95**(5):523-9. [Percutaneous retinoid absorption ... preview & related info | Mendeley](#)

Williams AL, Pace ND, DeSesso JM Teratogen update: Topical use and third-generation retinoids Birth Defects Research 2020 **112**(15):1105-1114.

WHO (2021) Vitamin A supplementation during pregnancy.

[https://www.who.int/elena/titles/vitamina\\_pregnancy/en/](https://www.who.int/elena/titles/vitamina_pregnancy/en/) (this link is no longer live).

Yee MMF, Chin K-Y, Ima-Nirwana S, Wong SK. Vitamin A and Bone Health: A Review on Current Evidence. Molecules 2021, **26**,1757.

Zachman RD, Grummer MA. The Interaction of Ethanol and Vitamin A as a Potential Mechanism for the Pathogenesis of Fetal Alcohol Syndrome. Alcoholism: Clinical and Experimental Research 1998; **22**(2): 1544 – 1556.

Zile MH Vitamin A and Embryonic Development: An Overview The Journal of Nutrition, 1998 128(2), 455S–458S <https://doi.org/10.1093/jn/128.2.455S>.

Zomerdijk IM, Ruiters R, Houweling LMA, Herings RMC, Sturkenboom MCJM, Straus SMJM, Stricker BH. Isotretinoin exposure during pregnancy: a population-based study in The Netherlands. BMJ Open 2014; **4**:e005602  
<https://doi.org/10.1136/bmjopen-2014-005602>.