

**CASE AND COMMENTARY: PEER-REVIEWED ARTICLE**

**Do You Know How to Assess Risks Posed by Over-the-Counter Vitamin A Supplements?**

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**Abstract**

Dietary supplements are regulated as foods by the US Food and Drug Administration (FDA) and, despite their potentially harmful effects, are not subject to labeling rules that apply to prescription medications. This commentary responds to a case about vitamin A supplement safety. The commentary compares regulation of vitamin A-derivative prescription medications, such as isotretinoin, to regulation of high-dose vitamin A supplements, illuminating both products' potential for causing birth defects. Label analysis is key to educating patients about risks of vitamin A-containing supplements. The commentary also suggests the need for more FDA oversight of the dietary supplement industry.

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**Case**

A 24-year-old woman asks a dermatologist about an acne supplement she purchased online. An advertisement for this product suggests that other products only cleanse the skin's surface, while this one is designed to prevent repeated breakouts of acne by making the immune system stronger. The product's label recommends 2 servings daily and specifies vitamin A content per serving as 1150% of the recommended dietary allowance of vitamin A in micrograms (mcg) of retinyl palmitate and beta-carotene. The dermatologist is concerned that this dose of vitamin A could be teratogenic, since isotretinoin is a vitamin A derivative requiring rigorous monitoring, especially to prevent birth defects. The patient asks, "Is this product safe?"

**Commentary**

The US Food and Drug Administration (FDA) defines a dietary supplement as a product taken by mouth that contains vitamins, minerals, herbs, botanicals, amino acids, and other ingredients intended to supplement a diet.<sup>1</sup> Acne is common among young adults, and several dietary supplements available online—including some containing high doses of vitamin A—claim to help treat it.<sup>2</sup> While vitamin A is an essential nutrient, high-dose

vitamin A dietary supplements can harm patients, given their teratogenic potential.<sup>2,3</sup> These supplements are widely available, have confusing labels, and lack the equivalent of a category X warning label,<sup>2,4</sup> so physicians should help patients understand these products' risks.

### Regulatory Differences

Potentially teratogenic prescription medications must include a package insert with pregnancy warning categories D or X, which indicate evidence of fetal risk. The FDA requires patients taking prescription isotretinoin (a category X derivative of vitamin A) who could become pregnant to comply with requirements of the iPLEDGE Program, which involves monthly pregnancy tests and multiple forms of birth control.<sup>5,6,7</sup> To emphasize this warning, isotretinoin packaging must prominently display multiple warnings against use during pregnancy.<sup>5</sup>

Dietary supplements are not subject to the same labeling and compliance standards that the FDA requires for prescription medications like isotretinoin,<sup>8,9</sup> which is a source of serious **clinical and ethical concern** for clinicians caring for patients consuming vitamin A dietary supplements available without a prescription. Unlike prescription drugs that must be proven safe and effective to receive FDA approval for sale in the US market, dietary supplements do not require FDA approval and are easy to buy and widely consumed.<sup>4</sup> The FDA may remove products from the market, but only if they are determined to be unsafe, adulterated, or mislabeled (ie, as treatment, prevention, or cure).<sup>10</sup>

### Vitamin A Safety

Consumers taking large doses of vitamin A are subject to the same risks of harm as patients taking prescription isotretinoin,<sup>3,5,7</sup> yet over-the-counter (OTC) vitamin A supplement labels are not required by the FDA to indicate risk of birth defects.<sup>2,4</sup>

*Assessing risk from amount.* One study found that, among acne products available online with potentially teratogenic doses of vitamin A, 2 products lacked a warning about these potential harms and 2 products recommended only to **consult a physician** prior to use if pregnant.<sup>2</sup> Supplement labels are required by the FDA to convey how much vitamin A a product contains. This is important, since one large study found that the ratio of the prevalence of cranial neural crest defects in babies born to women who took more than 10 000 international units (IUs) of preformed vitamin A daily during pregnancy to that of babies whose mothers took 5000 IUs or less was 4.8, indicating higher odds of such birth defects in babies born to women taking high doses of vitamin A during pregnancy, 1 in 57 of whom had a baby with a cranial neural crest defect.<sup>3</sup> These results are based on the numbers of IUs, while supplement labels typically display other units of measurement and thus require conversion to assess risk of harm.

*Assessing risk from form.* In addition to the number of IUs, the source, or form, of vitamin A is needed on a supplement's label. Dietary or supplemental sources of vitamin A provide either preformed vitamin A (ie, retinol and retinyl esters) or vitamin A precursors (ie, provitamin A carotenoids, including beta-carotene).<sup>11</sup> Labeling the percentage of preformed vitamin A and vitamin A precursors in a supplement is important because excess preformed vitamin A can be stored in the body and cause harm.<sup>3</sup> The risk of excess vitamin A *precursors*—including risk of teratogenicity in humans—is not known.<sup>3</sup> Despite the importance of the form of vitamin A, providing the

percentage of vitamin A supplied as preformed and precursor forms in nutrition labels is voluntary, according to FDA regulations.<sup>9</sup>

Another challenge in interpreting vitamin A dosage is that the units of measure need not be listed on the label. The recommended dietary allowance of vitamin A is currently reported not in IUs but in a measure called retinol activity equivalents (RAEs) by the Food and Nutrition Board,<sup>8,9,11</sup> and manufacturers are expected to use RAEs to calculate the percent daily value (% DV) on product labels. However, manufacturers are not required by the FDA to list the word *RAE* on supplement labels. Clinicians and consumers tend to assume that manufacturers comply with this labeling regulation but would have to perform calculations to confirm this supposition. If these sources of confusion are neither recognized nor resolved, it's impossible to accurately ascertain how much vitamin A is actually in a consumer's body and therefore impossible to accurately assess that consumer's risk of harm from vitamin A.

*Using amount and form to assess safety.* In the case, the vitamin A supplement label lists 10 500 mcg per serving from retinol palmitate (preformed vitamin A) and beta-carotene (a precursor) but does not specify whether 10 500 mcg means mcg RAE or mcg of retinol palmitate and beta-carotene. The only hint available on the label is the % DV, which is listed as 1167%. An extremely well-informed and health-literate consumer or a good clinician would try to confirm that the 10 500 mcg indicated on the label means 10 500 mcg RAE. To do this, one would need to know to look for—and find—in the Code of Federal Regulations the reference daily intake (RDI) for vitamin A: for adults and children aged 4 and older, it's 900 mcg RAE.<sup>9</sup> Multiplying 900 mcg by the DV (11.67) calculated from the % DV on the label, one could indeed confirm that 10 503 mcg RAE is close enough to the 10 500 mcg value indicated on the supplement's label.<sup>8,9</sup> The Table gives IU equivalents in mcg RAE and the teratogenic dose for different sources of vitamin A.

**Table.** IU Equivalents in mcg RAE and Teratogenic Dose for 3 Sources of Vitamin A<sup>a</sup>

	Source of vitamin A		
	Retinol <sup>b</sup>	Supplemental beta-carotene <sup>c</sup>	Dietary beta-carotene <sup>c</sup>
IU equivalent	0.3 mcg RAE	0.3 mcg RAE	0.05 mcg RAE
Risk of toxicity	> 3000 mcg RAE <sup>3</sup>	Unknown	Not applicable

Abbreviations: IU, international unit; RAE, retinol activity equivalent.

<sup>a</sup> Adapted from Office of Dietary Supplements.<sup>11</sup>

<sup>b</sup> Preformed vitamin A.

<sup>c</sup> Vitamin A precursor.

If one knows that a teratogenic dose of vitamin A is greater than 10 000 IU (3000 mcg RAE) of preformed vitamin A,<sup>3</sup> then one could question whether and to what extent the product poses risk of harm. A vitamin A supplement that contained 10 500 mcg RAE from preformed vitamin A would contain 35 000 IUs of vitamin A per serving.<sup>11</sup> Although this amount is a potentially dangerous dose for people who might be pregnant, especially during early gestation (eg, 7 weeks or earlier),<sup>3</sup> responsibility for considering the safety of OTC high-dose vitamin A supplements currently devolves upon consumers and clinicians, not the FDA or manufacturers.

### Need for Expanded Oversight

Consumers and clinicians can't know the risks posed by vitamin A supplements if they don't know or can't learn the amount of vitamin A active in a consumer's body when that supplement is used. Is it reasonable to expect that consumers and clinicians know how to assess risk of a vitamin A dietary supplement? Even assuming it is reasonable, one study found that for 5 of 26 vitamin A-containing acne supplements sold online, the IUs of vitamin A could not be calculated from information listed on the label or there was no specification of the form of vitamin A or the relative proportions of vitamin forms in the supplement.<sup>2</sup>

Due to vitamin A's teratogenic potential, the FDA should require manufacturers to label amounts of vitamin A in mcg RAE and percentages of vitamin A forms so that consumers and clinicians can quantify vitamin A amounts and assess risk.<sup>3,4</sup> We recommend that packaging of dietary supplements containing high doses of vitamin A provide pregnancy **warning labels**, that phrases such as "dermatologist formulated, tested, and approved" be clarified as insufficient evidence of a product's safety, and that adverse events from dietary supplemental vitamin A be reported by clinicians or consumers to the FDA's MedWatch program.<sup>12</sup>

In the case, the dermatologist should learn or calculate relevant clinical information about the amount of vitamin A in a dose of the supplement and educate the patient about those amounts' risks. At the policy level, the FDA should expand oversight of dietary supplements with teratogenic risk.

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