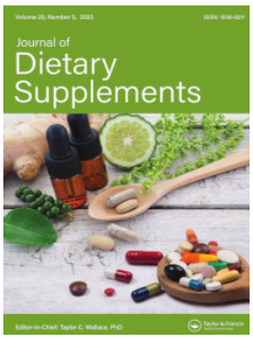

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RESEARCH ARTICLE

A Multi-Year Rancidity Analysis of 72 Marine and Microalgal Oil Omega-3 Supplements

Jacob M. Hands, BA[a], Mark L. Anderson, PhD[b], Tod Cooperman, MD[b] and Leigh A. Frame, PhD[c,d]

[a]The George Washington University School of Medicine & Health Sciences, Washington, District of Columbia, USA; [b]ConsumerLab.com, Vernon, New Jersey, USA; [c]Integrative Medicine, The George Washington University School of Medicine & Health Sciences, Washington, District of Columbia, USA; [d]Resiliency & Well-being Center, The George Washington University School of Medicine & Health Sciences, Washington, District of Columbia, USA

ABSTRACT

There exists significant heterogeneity in the 'freshness' of consumer marine- and plant-derived omega-3 (Ω3) supplements. Fears of rancidity, or the oxidation of consumer Ω3 supplements, has been debated in the literature with several prior authors reporting contradictory findings. We report the peroxide value (PV), para-anisidine value (p-AV) and total oxidation values (TOTOX) associated with 72 consumer Ω3 supplements sold in the United States sampled from 2014–2020. The effect of flavoring on the oxidation of the supplements was examined in an adjusted fixed effects model controlling for type of delivery system (enteric, liquid, animal- and vegetable-derived gelatin softgel, spray), source (algae, calamari, fish, krill, mussels), and certifications assigned by third-party organizations (e.g. USP). Overall, our results revealed that 68% (23/34) of flavored and 13% (5/38) unflavored consumer Ω3 supplements exceeded the TOTOX upper limit set by the Global Organization for EPA and DHA (GOED) voluntary monograph standard of ≤ 26, with 65% (22/34) flavored supplements and 32% (12/38) unflavored supplements failing the PV upper limit of ≤ 5 and 62% (21/34) flavored supplements exceeding the p-AV upper limit of ≤ 20. To our knowledge, no prior authors have modeled the impact of flavoring on oxidative status in 72 marine- and plant-derived Ω3 products sold in the U.S. We present our findings in this context and discuss the clinical implications related to the consumption of oxidized consumer fish oils and their effects on human health.

KEYWORDS

Fish oil; omega-3 fatty acids; plant; enteric; antioxidant; dietary supplement; nutraceutical; multivitamin

Introduction

Marine- and plant-derived omega-3 (Ω3) supplements containing EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) remain one of the most popular consumer supplements types with an estimated 16–33% of all U.S. households ingesting Ω3 in some supplemental form (Kamiński et al. 2020; Dietary Supplement Use Reaches All-Time High: Available-for-Purchase Consumer Survey Reaffirms the Vital Role

CONTACT Jacob M. Hands, BA jacobhands@gwu.edu 633 13th Street, Manhattan Beach, CA 90266, USA.

Supplementation Plays in the Lives of Most Americans 2019). As consumption of Ω3 products has increased, so too have concerns pertaining to their purity, potency, and stability in terms of rancidity. Accordingly, the total oxidative status of consumer Ω3 products (rancidity) has become a significant source of controversy with interest groups arguing that a majority of Ω3 supplements are unacceptably oxidized and therefore pose significant health risks. Currently, recommended rancidity limits are voluntarily maintained according to a monograph set forth by the Global Organization for EPA and DHA Omega-3s (GOED), a cross-national organization deriving from the Council for Responsible Nutrition (The GOED Voluntary Monograph 2023). At present, GOED monograph standards set forth relatively conservative oxidation limits for consumer Ω3 products containing EPA and DHA that are, in fact, vastly more stringent than those governing other oils including vegetable and fruit oils such as extra virgin olive oil (Ismail et al. 2016). Specifically, GOED standards articulate generally acceptable limits pertaining to the primary oxidation of consumer fish oils, peroxide value (PV), and the sum of all secondary oxidative products, or the para-anisidine value (p-AV). These products are adduced (2PV + p-AV) to create the arbitrary TOTOX, or 'total oxidation' value used as an indication of rancidity. As Shahidi and Zhong note, the interpretation of TOTOX is complex in that it is not a 'scientific value' but rather an amalgamation of two laboratory values with different dimensions and units that is commonly used to describe the overall oxidation of a sample (Shahidi and Zhong 2005). GOED voluntary monograph limits PV to a maximum value of 5 meq/kg, p-AV to a maximum of 20, and TOTOX to a maximum of 26. Flavored oils are an anomaly with regard to calculating a TOTOX value as added flavoring, synthetic or natural, can, in some cases falsely elevate p-AV and therefore produce unreliable measures of oxidation. Prior reviews have reported varying degrees of compliance with GOED guidelines; though, notably, recent analyses have demonstrated marked increases in rates of adherence to GOED limits and a trend toward lower oxidation (Bannenberg et al. 2020; De Boer et al. 2018; Kleiner et al. 2015; Sprague et al. 2018; Srigley and Rader 2014).

As prior authors have noted, the structure of polyunsaturated fatty acids (PUFA) renders them particularly vulnerable to oxidation (Albert et al. 2013). The position of the carbons (bisallylic), in addition to the sheer number of double bonds, facilitates hydrogen loss, a function of low activation energy and subsequent peroxide formation. Initial peroxidation can promote chain reactions, particular in the presence of catalytic elements – such as heat, oxygen, light, and metallic ions – resulting in the formation of various species of hydroperoxides and conjugated dienes and trienes with different chemical properties resulting from rearrangements in shape and polarity (Albert et al. 2013; Shahidi and Zhong 2005). The sum of these peroxide derivatives, or hydroperoxides, constitute the PV. Of note, the PV of a sample initially exceeds the rate of its decomposition at the early stages of oxidation. However, as the sample is further oxidized, the rate of decomposition exceeds peroxide formation and thus the PV can appear deceptively low (Shahidi and Zhong 2005). Hydroperoxides continue to metabolize into secondary oxidation products. These secondary oxidation products can largely be classified as aldehydes. Indeed, the p-AV test chiefly measures the presence of 2-alkenals and 2,4 alkandienals, which represent the cumulative secondary oxidative products (Ismail et al. 2016; Shahidi and Zhong 2005).

Importantly, PV and p-AV interpretation should be met with caution. p-AV, in particular, can be falsely elevated in the presence of natural or synthetic flavorings and pigments. As the p-AV assay is a colorimetric method, aldehydes present in these flavorings can interfere with the measurement in finished products. As Ismail et al. (2016) has referenced, lemon flavorings, for example, can increase p-AV concentrations more than 12x (De Boer et al. 2018; Ismail et al. 2016; Shahidi and Zhong 2005). Similarly, Ye et al. (Ye et al. 2020) determined that certain flavorings such as chocolate-vanillin, lemon, citrus, and bubblegum contribute most significantly to the elevation in p-AV and thus may confound rancidity analysis. Moreover, as Shahidi and Zhong (Shahidi and Zhong 2005) documented, p-AV can present falsely high values even in 'fresh' samples owing to higher PUFA content. Furthermore, certain oils, such as those sourced from krill and salmon have unique properties rendering them less suitable for colorimetric analysis. Krill delivers Ω3 in a phospholipid vehicle, hence, is naturally polar and thus is often reported as falsely elevated on p-AV testing. Similarly, the presence of pigmented compounds such as carotenoids, specifically astaxanthin, in salmon can interfere with the measurement. The contribution of such flavorings and colorings, as Bannenberg et al. described, may be a parsimonious explanation for perceived rates of non-alignment with GOED rancidity limits (Bannenberg et al. 2020). The GOED monograph states that the p-AV assay is not applicable to flavored oils due to such inaccuracies. While it is well documented that flavorings can produce falsely elevated p-AV, the magnitude of the p-AV increase varies depending on the flavor and the amount used. This data shows that 20.6% of flavored products had a p-AV value ≤ 20 a PV ≤5 and an acceptable TOTOX value calculated within GOED guidelines. Therefore, the p-AV of flavored fish oils should be interpreted with caution but, in some cases, can still be calculated in alignment with GOED guidelines and may be considered applicable depending on the product (Ye et al. 2020). Regarding TOTOX values in general, prior reviews have reported varying degrees of alignment with GOED recommendations; though, notably, recent analyses have demonstrated marked increases in rates of adherence to GOED limits and a trend toward lower oxidation (Bannenberg et al. 2020; De Boer et al. 2018; Kleiner et al. 2015; Sprague et al. 2018; Srigley and Rader 2014).

The aim of this study is to assess the impact of flavoring on oxidative status in marine- and plant-derived Ω3 products containing EPA and DHA with respect to GOED guidelines and to provide a partial view of the oxidative landscape of the US, Ω3 supplement market. Though manufacturers are more commonly disclosing the oxidative status of their products, it may be of consumer value to begin encouraging marine and algae derived omega-3 oil manufacturers to voluntarily disclose the oxidative status of their product.

Methods and statistics

We tested and analyzed 72 consumer Ω3 oil supplements to assess their oxidative status in 4 'cohorts' from 2014–2020. Each cohort contained 11–24 supplements evaluated for PV, p-AV and TOTOX. Various delivery systems included capsule type

(enteric-coated gel, liquid, animal- or vegetable-derived gelatin softgel, spray), oil source (algae, calamari, fish, krill, mussels) and third-party certifications (cGMP, iFOS, USP). For fish, this included anchovy, mackerel, and sardine, which are typical. However, some companies are beginning to switch to salmon and specialty types. All supplements were purchased from third party online retailers (e.g. Amazon, iHerb), physical distributors (e.g. GNC) and manufacturer websites between August through December of their listed year. All products were domestically produced and bought.

Supplements were selected according to a year ranked product survey taken by 8000–10,000 respondents through the online site, ConsumerLab.com, an independent testing company committed to providing transparency and clinically-guided knowledge of nutritional supplementation to consumers and healthcare providers. Two independent commercial laboratories in the domestic U.S. were enlisted for analysis – a separate validation test was conducted for all samples exceeding any pre-specified oxidative threshold. Any sample failing its initial specifications was retested at one of two independent labs for confirmation.

The Ω3 assays were performed in accordance with AOAC 991.39 standards *via* gas chromatography. Peroxide (PV), para-anisidine (pAV) values and calculation of TOTOX were determined by AOCS method (CD 8b-90 & 18–90 respectively) or other methods as appropriate (Latimer 2023). 'Acceptable' oxidative-quality criteria for the Ω3 supplements tested were PV ≤ 5, pAV ≤ 20, and TOTOX ≤ 26, as specified by the GOED (The GOED Voluntary Monograph 2023).

Initially, flavored and unflavored products, as well as those sourced from algae versus those from other sources, were crudely compared using Welch's T-test to account for disparate sample types and sizes. A fixed effects model with robust standard errors was subsequently employed to predict the contribution of flavor to TOTOX, controlling for capsule type, oil source, and third-party certification by year. Appropriateness of the model was ascertained *via* Hausman testing for endogeneity, which revealed no significant superiority between a fixed and random effects model. However, fixed effects were ultimately selected due to the nature of the longitudinal data. Similarly, the Breush and Lagrange Pagan multiplier test was employed to assess the suitability of ordinary least squares (OLS). Again, the results supported simple OLS regression, which was abandoned due to the nature of our longitudinal data. OLS testing and fixed effects modeling revealed similar findings and are included as robustness checks. Subsequent pairwise t-testing (Tukey) was undertaken to evaluate significant variation in supplement oxidation between 2014–2020. Median testing was employed as a robustness check. All statistics were calculated using StataBE 17, StataCorp (College Station, TX).

Results

The TOTOX, PV, and p-AV of 72 consumer Ω3 oil supplements distributed by 52 unique companies were evaluated from 2014–2020. Supplements in this sample were sourced from fish (57), algae (10), krill (1), calamari (2) and mussel (2).

From 2014–2020, the median peroxide value of all products tested was 7.81 mEq O_2/kg. The p-AV median was 23.47 with a mean of 10.9. Median TOTOX from

Table 1. Summary statistics.

	N	Mean	Median	Min	Max
TOTOX	72	38.571	21.8	3.7	240.5
Peroxide	71	7.81	5	0	50
p-Av	71	23.47	10.9	0	209.9
TOTOX (2020)	13	58.246	38.3	11.3	223.3
TOTOX (2018)	11	22.5	18.8	4.8	60.8
TOTOX (2016)	24	43.921	26.6	7.3	240.5
TOTOX (2014)	24	29.929	19.75	3.7	104.3
Perox (flavored)	33	10.08	6.7	0	50
p-Av (flavored)	33	40.64	31.2	2.4	209.9
TOTOX (flavored)	34	59.074	52.2	3.7	240.5
Perox (no flavor)	38	5.84	4.4	0	33
p-Av (no flavor)	38	8.55	8.1	0	14.5
TOTOX (no flavor)	38	20.226	18.05	5.9	66
TOTOX (fish)	57	40.965	23.5	3.7	240.5
TOTOX (algae)	10	12.87	11.4	7.3	23.7
TOTOX (enteric)	6	32.967	28.45	11.3	56.6
TOTOX (not enteric)	66	39.08	21.8	3.7	240.5
TOTOX (certified)	11	26.864	18.8	9.6	73.2
TOTOX (not certified)	57	38.565	23.5	3.7	240.5

2014–2020 was 21.8 and the mean was 38.57 (Table 1). Median and mean TOTOX values, respectively, were calculated for Ω3 supplements sourced from fish (40.97, 23.5), algae (12.87, 11.4), enteric-coated supplements (32.97, 28.45), non-enteric coated supplements (39.08, 21.8), supplements with at least one certification (26.86, 18.8), and supplements without any certification (38.57, 23.5) (Table 1).

Among non-flavored supplements, 87% (33/38) met GOED criteria for TOTOX of ≤26, while only 32% (11/34) met the same criteria among flavored products. With respect to the peroxide value of unflavored products, 68% (26/38) met the criteria for PV ≤ 5. Among flavored products, 35% (12/34) met the criteria of PV ≤ 5. The p-AV criteria of ≤20 was achieved in 100% (38/38) unflavored products, whereas 6% (4/34) of flavored products met the same standard.

The mean TOTOX differed significantly between flavored products and unflavored products (20.22 versus 59.074 t = .3.97, Pr(T< t) = 0.002) (Tables 2–4). PV values also differed significantly between flavored and unflavored products (10.08 versus 5.84, t = −1.76, Pr(T<t) = 0.04). p-AV testing between flavored and unflavored products demonstrated a similarly significant disparity (40.64 versus 8.55, t = −4.05, Pr (T < t) = 0.002). A similar finding of significant differences in TOTOX was noted between products sourced from algae and those sourced from fish, krill, calamari, or mussels (42.71 versus 12.87, $t = 4.95$, Pr(T > t) = <0.0001). There were no significant differences in the TOTOX associated with enteric versus non-enteric Ω3 oil supplements. Significant differences could not be confirmed between delivery methods (e.g. type of softgel, liquid, spray, vegetarian, chewable) owing to limited sample size.

Adjusted fixed-effect modeling revealed a statistically significant increase in the TOTOX associated with flavored products (20.67, 95% CI [9.33–32.02], $p = 0.01$) (Tables 1 & 2). Subsequent pairwise t-testing to assess the effect of 'batch' year on oxidative status yielded a non-significant increase in the TOTOX comparing years 2020 to 2014 (17.6 (9.50), $t = 1.85$, $p = 0.26$) and 2020 to 2018 (22 (10.96), $t = 2.01$, $p = 0.197$) (Tables 1, 5). Of note, median testing was leveraged as a robustness check

Table 2. Regression results (fixed, random effects robust SEs).

Variables	TOTOX (random effects)	TOTOX (fixed effects)
Flavor	20.50***	20.67**
	(2.155)	(3.566)
Certified	−4.984*	−2.128
	(2.737)	(3.358)
Enteric	−107.4	−114.2
	(77.91)	(73.42)
Liquid	−103.9	−106.6
	(79.87)	(77.82)
Softgel	−105.6	−107.1
	(80.08)	(79.40)
Spray	82.62	66.07
	(78.09)	(76.79)
Vegetarian	−110.2	−112.7
	(74.46)	(72.90)
Calamari	72.78**	71.64*
	(29.15)	(30.11)
Fish	12.69**	11.44
	(6.118)	(5.218)
Krill	54.09***	47.30**
	(4.088)	(9.090)
Mussel	9.089*	9.552*
	(4.845)	(3.747)
Observations	72	72
R-squared		0.625
Number of year	4	4

Robust standard errors in parentheses.
***$p < 0.01$, **$p < 0.05$, *$p < 0.1$.

Table 3. Regression results (robust with fixed effects).

TOTOX	Coef.	St.Err.	t-value	*p*-value	[95% Conf	Interval]	Sig
Flavor	20.673	3.566	5.80	.01	9.325	32.022	**
Certified*	−2.128	3.358	−0.63	.571	−12.814	8.558	
Vehicle Type							
Enteric	−114.157	73.417	−1.55	.218	−347.801	119.488	
Liquid	−106.623	77.822	−1.37	.264	−354.288	141.043	
Softgel	−107.086	79.397	−1.35	.27	−359.761	145.589	
Spray	66.07	76.788	0.86	.453	−178.304	310.445	
Vegetarian	−112.708	72.904	−1.55	.22	−344.72	119.305	
Source							
Calamari	71.643	30.106	2.38	.098	−24.168	167.454	*
Fish	11.443	5.218	2.19	.116	−5.164	28.05	
Mean dependent var		38.571	SD dependent var			43.735	
R-squared		0.625	Number of obs			72.000	
F-test		.	Prob > F			.	
Akaike crit. (AIC)		677.128	Bayesian crit. (BIC)			683.958	

***$p < .01$, **$p < .05$, *$p < .1$.
*Certified refers to any certification statement including iFOS or cGMP.

and yielded a significant variation in medians ($chi^2 > 9.26$, $p = 0.03$) (Table 6). The Tukey method was selected for interpretation (Table 7). Significant differences by oil source are observed in the adjusted model; however, these findings are immaterial owing to limited sample size and inherent limitations on testing associated with flavored oils and those delivered in phospholipid form.

Table 4. Peroxide (2014-2020) Two-sample t test with unequal variances

Group	Observations	Mean	Std. err.	Std. dev.	[95% Conf Interval]
No Flavor	38	5.837	0.992	6.115	3.827 – 7.847
Flavor	33	10.078	2.199	12.633	5.596 –14.55
Combined	71	7.807	1.170	9.862	5.472 – 10.141
Diff	–	−4.239	2.412		−9.097 – 0.619
T-stat	−1.757	Pr (T < t)	0.043	–	
pAV (2014-2020) Two-sample t test with unequal variances					
Group	Observations	Mean	Std. err.	Std. dev.	[95% Conf Interval]
No Flavor	38	8.552	0.557	3.435	7.423 – 9.682
Flavor	33	40.639	7.907	45.422	24.534 – 56.745
Combined	71	23.466	4.127	34.773	15.236 – 31.697
Diff	–	−32.087	7.926		−48.226 – -15.947
T-stat	−4.048	Pr (T < t)	0.0002	–	
TOTOX (2014-2020) Two-sample t test with unequal variances					
Group	Observations	Mean	Std. err.	Std. dev.	[95% Conf Interval]
No Flavor	38	20.226	1.941	11.966	16.293 - 24.159
Flavor	34	59.074	9.601	55.983	39.539 – 78.607
Combined	72	38.571	5.154	43.735	28.293 – 48.848
Diff	–	−38.847	9.795		−58.716 – -18.979
T-stat	−3.966	Pr (T < t)	0. 0002	–	

Table 5. Oxidative status by year.

Year	N	Mean	Median	Min	Max
2014					
PV	24	5.992	4.9	0	44
p-AV	23	18.726	10.7	3.7	57.8
TOTOX	24	29.929	19.75	3.7	104.3
2016					
PV	24	12.517	7.95	1.4	50
p-AV	24	18.887	10.5	0	140.5
TOTOX	24	43.921	26.6	7.3	240.5
2018					
PV	10	4.36	3.85	2.5	8.9
p-AV	11	14.355	10.7	2.4	43
TOTOX	11	22.5	18.8	4.8	60.8
2020					
PV	13	5.115	4.7	1.9	12
p-AV	13	48.015	28.4	3.7	209.9
TOTOX	13	58.246	38.3	11.3	223.3

Table 6. Median test (TOTOX).

	Year				
Greater than the median	2014	2016	2018	2020	total
no	15	8	9	5	37
yes	9	16	2	8	35
Total	24	24	11	13	72

Table 7. Tukey pairwise T-Testing (TOTOX).

Year	Std	Err.	t	P > t
2016 vs 2014	2.769	8.202	0.340	0.987
2018 vs 2014	−4.386	9.771	−0.450	0.970
2020 vs 2014	17.606	9.500	1.850	0.259
2018 vs 2016	−7.155	9.855	−0.730	0.886
2020 vs 2016	14.837	9.586	1.550	0.416
2020 vs 2018	21.992	10.959	2.010	0.197

Discussion

The results of batch testing 72 Ω3 supplements from 2014–2020 found 54.2% (39/72) of the samples exceeded one or multiple GOED specifications for rancidity. We preface our analysis by cautioning that products exceeding voluntary GOED oxidative thresholds may not necessarily imply true 'rancidity' and instead owe to random variation associated with sample selection and limitations associated with p-AV testing of flavored oils. As previous authors have noted and as delineated above, p-AV is a corruptible measurement, liable to alterations associated with natural and artificial color, flavoring, and PUFA concentration (De Boer et al. 2018; Ismail et al. 2016; Shahidi and Zhong 2005). Indeed, amongst flavored supplements, we observed a statistically significant association of flavor with increased TOTOX, even adjusting for confounding variables. Some of the discrepancy in TOTOX between flavored (59.07) and unflavored products (20.22) could be attributed to the nearly 32.1 unit increase in p-AV associated with flavored products. It should be noted, however, that the PV was significantly higher amongst supplements with added flavoring, possibly due to the degradation and/or oxidation of the flavoring itself ($p = 0.04$). Flavored products remain an anomaly regarding P-AV, PV, and TOTOX values. These products are anecdotally popular with consumers wishing to avoid 'fishy taste', yet GOED guidelines state the p-AV assay is not applicable to flavored products because it may interfere with rancidity testing. However, if this exempts flavored oils from testing it could be creating a loophole for spoiled products to make it to market. The data presented here shows that roughly 32% (11/34) of flavored products produce an acceptable TOTOX value in alignment with GOED guidelines indicating the flavoring in the setting of a p-AV assay may not necessarily confound the acceptability of flavored products.

The question of the health 'risks' posed by the consumption of oxidized Ω3 oil is, in fact, still unresolved. Prior authors have contended and demonstrated that oxidized PUFAs may display altered, perhaps adverse, biological activity in human subjects in comparison with less oxidized PUFA (Albert et al. 2013; García-Hernández et al. 2013; Haglund et al. 1991). In particular, previous studies evaluating the effect of oxidation on traditional markers of fish oil efficiency have demonstrated conflicting results. An *in vitro* experiment investigating the influence of oxidized fish oil versus a 'non-oxidized' counterpart on the sd-LDL subfractions found that oxidized PUFA were inferior to non-oxidized counterparts at effectively inhibiting sd-LDL oxidation (33% versus >90%) (Mason and Sherratt 2017). Similarly, human trials comparing oxidized and less oxidized fish oil consumption have generated intriguing results. A trial involving healthy 18–50 year old subjects exposed to oxidized fish oil, high quality fish oil, or high oleic sunflower oil demonstrated significant, adverse effects on lipoprotein subfractions after 7 wk of high oleic sunflower and oxidized fish oil supplementation in comparison with high quality fish oil consumption (Rundblad et al. 2017). Furthermore, a trial involving 52 women randomly assigned to oxidized versus non-oxidized fish oil supplementation with dietary intervention for 30 days found that oxidized fish oil supplementation failed to significantly reduce cholesterol and blood pressure, while consumption of non-oxidized fish oil significantly lowered systolic, diastolic blood pressure as well was as total cholesterol (García-Hernández et al. 2013). Interestingly, the non-oxidized group showed a statistically significant increase in fasting blood sugar

within technically euglycemic, though pre-diabetic, parameters. Trials such as the above suggest that the biological affects mediated by oxidized consumer fish oil supplements are complex and may warrant caution.

Yet, famously, among 83 subjects randomized to ingest 8 grams per day of unflavored, oxidized fish oil (TOTOX = 45), unoxidized fish oil (TOTOX = 11), and high oleic sunflower oil (TOTOX = 11) for 3–7 wk showed no significant changes in markers of lipid peroxidation, systemic inflammation, or oxidative stress. Though, similar increases in plasma EPA and DHA were observed (Ottestad et al. 2012). A post hoc analysis of this cohort revealed oxidized fish oil supplementation was not associated with significant differences in markers of atherosclerotic risk such as ICAM, VCAM, IL-6, nor oxidized LDL; though, ICAM appeared to decrease in the higher quality fish oil group and bordered on significance after 7 wk. It may be of importance that the driver of high TOTOX in the oxidative supplement cohort appeared to be the strikingly high PV (18) of the supplement. Hydroperoxides are the primary constituent of the PV and constitute the first products of oxidation, whereas p-AV is typically thought of as the accumulation of secondary oxidation products, such as aldehydes, including malondialdehyde (MDA), which have been more notably associated with DNA damage and atherogenicity (Ottestad et al. 2012). A trial involving 30 mL consumption of vitamin E-infused fish oil versus a non-vitamin E-infused oil found that the non-vitamin E-infused cohort displayed an attenuated capacity to reduce serum triglycerides along with promoting a significant increase in serum MDA (Haglund et al. 1991). At present, vitamin E in addition to various antioxidant blends (e.g. mixed tocopherols, rosemary extract) are largely standard among current consumer fish oil products, and, thus, this finding may no longer be of interest (Haglund et al. 1991). Indeed, as Ismail et al. has remarked, extensive trials evaluating MDA or F_2 Isoprostane changes associated with EPA and DHA consumption have failed to produce significant findings (Ismail et al. 2016).

It may seem surprising that some investigators have found beneficial effects associated with the intake of oxidized oils with respect to the resolution of inflammatory processes in the body (Brooks et al. 2011; Mishra et al. 2004). In fact, as prior authors have noted, oxidized fish oil metabolites and endogenous peroxides, including those derived from EPA, also exert beneficial effects *in vivo* such as the inhibition of NF-kB in macrophages and decreases in monocyte chemoattractant protein-1 (MCP-1) (Brooks et al. 2011; Mishra et al. 2004). In addition, there is scant evidence to suggest that the consumption of oxidized oils necessarily translates into an increase in oxidative metabolic products, especially in the context of first-pass metabolism by the liver (Ismail et al. 2016). Fish consumption, even when cooked (though, perhaps, not when fried), is advocated by numerous organizations and has been linked to beneficial health outcomes, especially in the realms of cardiovascular disease and cognitive decline (Kosti et al. 2022; Qin et al. 2014; Zhang et al. 2020). Of note, various factors can alter the 'rancidity' of an oil sample including harvesting practices of the fish being sourced such as bleeding, antioxidant content of the feed, and preparation methods (Secci and Parisi 2016). Moreover, edible oils are often refined which can lead to significant decreases in the content of oxidized fatty acids and secondary oxidation products

Finally, adverse effects owing to highly oxidized samples may not necessarily reflect the oxidative status of the oils themselves. For example, PUFA (including EPA and DHA) content varies considerably amongst fish oil supplements as does the concentrations of

saturated fat, including palmitic acid (16:0) and myristic acid (14:0). Each saturated fat listed, among other fatty acids generally present in unspecified concentration, are known to raise circulating atherogenic lipoprotein subfractions, such as LDL, and therefore may confound analyses that attempt to estimate the risks associated with Ω3 supplementation (Bannenberg et al. 2020, García-Hernández et al. 2013, Mason and Sherratt 2017, Sprague et al. 2018; Kleiner et al. 2015; Latimer 2023; Most Popular Dietary Supplements 2022).

Conclusion

In this analysis, we report the oxidative status of 72 consumer Ω3 supplements from 2014–2020. Our results demonstrate varied, if nuanced compliance with GOED standards. The implications associated with these findings are delineated. Overall, the oxidative state of the consumer Ω3 products tested is not, at this time, a demonstrated hazard.

Authors' contributions

Jacob M. Hands (JMH) wrote and drafted this manuscript in partnership with Dr. Mark L. Anderson (MLA), Dr. Tod Cooperman (TC), and Dr. Leigh A. Frame (LAF). MA, TC, and LAF reviewed the manuscript extensively and contributed to its design. JMH drafted the statistics. MA and TC approved, designed and contributed to the intellectual outline of this piece from statistical outline to conceptual overview.

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About the authors

Jacob M. Hands is a medical student at the George Washington University School of Medicine and Health Sciences. Mr. Hands worked as a clinical research associate, contract research assistant to various companies, and continues to be an active member of the NLA and other affiliates.

Dr. Mark L. Anderson is the Vice President for Research at ConsumerLab.com. Dr. Anderson has over 28 years of experience in dietary supplement research in addition to 10 years of experience in pharmaceutical and biotechnology drug development. He has been actively involved in analytical testing, utilizing methods such as HPLC, ELISA, CPC, GC, GC/MS, SEC, IEF, LC/MS/MS and has developed and validated qualitative and quantitative assays in accordance with GLP/GMP regulations. Dr. Anderson has authored over 10 peer-reviewed publications in pharmacology and analytical chemistry and is an active member of AOAC International, serving as an elected member of the Executive Committee in the Technical Division on Reference Materials. He was previously the Director of Research & Development at Triarco Industries. Earlier in his career, Dr. Anderson held positions as Analytical Laboratory Director at Emisphere Technologies, Associate

Senior Scientist at Purdue-Frederick Pharmaceutical Co, and a Clinical Laboratory Technologist in Toxicology at Metpath Laboratories. Dr. Anderson received his Ph.D. in Pharmacology/Toxicology from St. John's University.

Dr. Tod Cooperman is a nationally recognized and respected researcher, writer, and speaker on consumer healthcare issues and is the President of ConsumerLab.com LLC and CEO of PharmacyChecker.com LLC. Dr. Cooperman is a graduate of the Boston University School of Medicine, receiving his M.D. in 1987. He also received his Bachelor's degree from Boston University with a major in Medical Sciences and a minor in Economics. Recognizing a lack of quality standards and oversight in the U.S. dietary supplement industry, Dr. Cooperman founded ConsumerLab.com in 1999, guiding it to become the leading independent evaluator of dietary supplements and nutritional products. Dr. Cooperman has been called as an expert witness by committees of U.S. House of Representatives and U.S. Senate to give testimony regarding the quality and regulation of dietary supplements and has been regularly invited to speak about dietary supplement quality at the National Institutes of Health.

Dr. Leigh Frame brings nutrition and immunity together through clinical, translational research. Her T-shaped expertise in health, wellness, science, and medicine was developed through her wide-ranging experience in biomedical research (from wet bench to clinical research) and overseeing research and education programs.

Dr. Frame is building a GW Integrative Medicine research program while directing the graduate education programs and the Office of Integrative Medicine and Health. She is also co-founder and Associate Director of the GW Resiliency & Well-being Center. Her interests include the role of the microbiome and nutrition in health, the consequences of malnutrition in obesity, vitamin D as an immune-modulatory hormone, research ethics, science communication, whole person care, resiliency, and well-being.

While working at the Johns Hopkins Center for Bariatric Surgery, Dr. Frame earned her PhD in Human Nutrition from the Johns Hopkins Bloomberg School of Public Health and received a Master of Health Science in Molecular Microbiology and Immunology from the same school. Dr. Frame earned Distinction in Biochemistry from Mary Baldwin College (now University).

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