WHO summary on the available evidence for the essential fatty acid profiles in ready-to-use therapeutic foods for treating children with severe wasting

The World Health Organization (WHO) commissioned a systematic evidence review regarding the composition of essential fatty acids (EFA) in ready-to-use therapeutic foods (RUTF) following concerns that the fatty acid profiles of the standard RUTF in the Joint Statement[1] do not support optimal brain development.

The review question was framed in the PICO (population, intervention, control, and outcomes) format as follows: does provision of RUTFs with fatty acid profiles that are different from specifications in the Joint Statement (i.e., with increased alpha-linolenic acid (ALA) and/or decreased linoleic acid (LA)) improve outcomes such as neurodevelopment in children aged 6 months or older recovering from severe wasting?

Summary of Findings

The evidence was derived from three randomized controlled trials (RCT) conducted in Malawi (2 trials) and Kenya. Two trials provided high oleic peanut to improve the amount of ALA in the RUTF (HO-RUTF) (Hsieh et al.,2015; Stephenson et al., 2021). Stephenson et al. (unpublished) also added a third study arm with a HO-RUTF with added docosahexaenoic acid (DHA) supplementation (DHA-HO-RUTF). The third trial provided two interventions: i) a flaxseed oil containing RUTF, and ii) a flaxseed oil containing RUTF with additional fish oil capsules containing EPA and DHA (Jones et al., 2015).

Neurodevelopment

Only one study (Stephenson et al., unpublished) assessed neurodevelopment as a primary outcome using the Malawi Developmental Assessment Tool (MDAT) global development, and problem-solving assessment (PSA) scores including, fine motor, gross motor, social and language development. There were significantly higher scores of the global assessment and the gross motor domains in children receiving DHA-HO-RUTF compared with the standard formulation 6 months after follow-up (mean difference: 0.19 (0.0, 0.38), 0.29 (0.03 to 0.55)) respectively but no differences were observed in these domains between HO-RUTF and the standard formulation. Both intervention arms had significantly higher scores in the social domain compared with the standard formulation (0.16 (0.00 to 0.31) for DHA-HO-RUTF and 0.24 (0.09 to 0.40) for HO-RUTF). No differences were observed for the following developmental outcomes: fine motor, language, problem-solving, intention scores or the eye-tracking.

Plasma essential fatty acids

There was higher LA composition in children receiving standard RUTF compared to children receiving alternative RUTF (overall mean difference: -0.83 [-1.48, -0.18], $Chi^2 = 0.19$, $P = 0.01$, $I^2 = 0\%$) (Annex 1).

There was higher ALA composition in children consuming RUTF formulations with altered EFA compared to standard RUTF with an overall mean difference: 0.23 [0.18, 0.28], $Chi^2 = 0.96$ ($P < 0.0001$, $I^2 = 0\%$) (Annex 2). ALA composition did not significantly differ between studies with lower omega 6: omega 3 PUFA ratio RUTF and those with RUTF with omega 3 LCPUFA.

[1] WHO, UNSCN, UNICEF. Community-based management of severe acute malnutrition. A joint statement by the World Health Organization, World Food Programme, United Nations Standing Committee on Nutrition, United Nations Children's Fund. Geneva, World Health Organization. 2007.

Arachidonic acid compositions were on average higher in children receiving standard RUTF compared to RUTF formulations with altered EFA but a relatively high heterogeneity was observed (overall mean difference: -0.73 [-1.22, -0.24], $Chi^2 = 8.5$, P = 0.004, I^2 77%) (Annex 3).

Plasma phospholipid EPA compositions were higher in children receiving RUTF formulations with altered EFA compared to the standard formulation (overall mean difference: 0.20 [0.15, 0.25], $Chi^2 = 15.3$, P < 0.00001, I^2=87%) (Annex 4). EPA composition did not significantly differ between studies with lower omega 6: omega 3 PUFA ratio RUTF and those with RUTF with omega 3 LCPUFA.

The omega 6 docosapentaenoic acid composition was higher in children receiving the standard RUTF compared to the two arms of DHA-HO-RUTF and HO-RUTF (overall mean difference: -0.07 [-0.11, -0.04], $Chi^2 = 0.32$, P < 0.0001, I^2=0%) (Annex 5). The omega 6 docosapentaenoic acid composition did not show subgroup differences between the lower omega 6: omega 3 ratio RUTF and the RUTF with omega 3 LCPUFA.

The DHA composition was higher in children receiving formulations that had added DHA compared to standard RUTF, but heterogeneity was high (overall mean difference: 0.33 [0.15, 0.50], $Chi^2 = 18.7$ P = 0.0003, I^2=89%) (Annex 6).

One study (Jones *et al.*, 2015) also reported erythrocyte fatty acid status where it was demonstrated that the FFO-RUTF flaxseed RUTF with fish oil (FFO-RUTF) and the flaxseed RUTF (F-RUTF) groups had a higher DHA composition compared with the standard formulation (6.3 (6.02-7.33), 4.51(3.92-4.85), vs. 3.88 (2.36-5.70), P ≤ 0.001), whilst only the FFO-RUTF group had a higher DHA composition at the end of the 84 days compared with baseline composition (P ≤ 0.001). The omega 6 PUFA: omega 3 PUFA and omega 6 LCPUFA: omega 3 LCPUFA ratios were lower in both the FFO-RUTF and F-RUTF arms compared with those of the standard RUTF arm (2.03 (1.90-2.23), 3.23 (3.06-3.77) vs. 4.48 (3.22-6.12), P ≤ 0.001 and 1.2 (0.99-1.36), 1.97 (1.77-2.23) vs. 2.76 (1.96-3.80), P ≤ 0.001). Furthermore, the endline omega 6 LCPUFA: omega 3 LCPUFA ratio was significantly higher compared with baseline ratios of the standard RUTF arms (P ≤ 0.01), but the opposite was true for the FFO-RUTF arm (P ≤ 0.001).

Costs and feasibility

Data on costs and feasibility were scanty but it was estimated that the high oleic vegetable oils may cost 10% more compared with traditional vegetable oils (Stephenson *et al.*, 2021).

A quick survey of UNICEF's RUTF suppliers base was conducted to collect feedback on the feasibility and implications of altering their RUTF formulations to accommodate the new proposed limits of omega 3 and omega 6 fatty acids.
Out of 20 RUTF suppliers contacted, 17 reported that the proposed levels of omega 3 and omega 6 fatty acids would be feasible and can be achieved in their existing production. When the suppliers were asked if the change would result in an increased cost, there was considerable variability in responses with some suppliers saying there will be no cost increase, some reporting minimal cost increase while others estimating up to 20% potential cost increase.

UNICEF also contacted three major suppliers of preformed DHA to request for estimated costs if marine DHA sources were added to RUTF in two different dosage scenarios. On average, amending the current RUTF essential fatty acid profile by reducing the omega 6 level and increasing the omega

3 level may increase the production cost by an additional US $0.02 per sachet. Adding preformed DHA to RUTF may results in a cost increase of US $0.02 – US $0.03 per sachet, depending on the dose (72mg/100g RUTF or 104mg/100g RUTF).

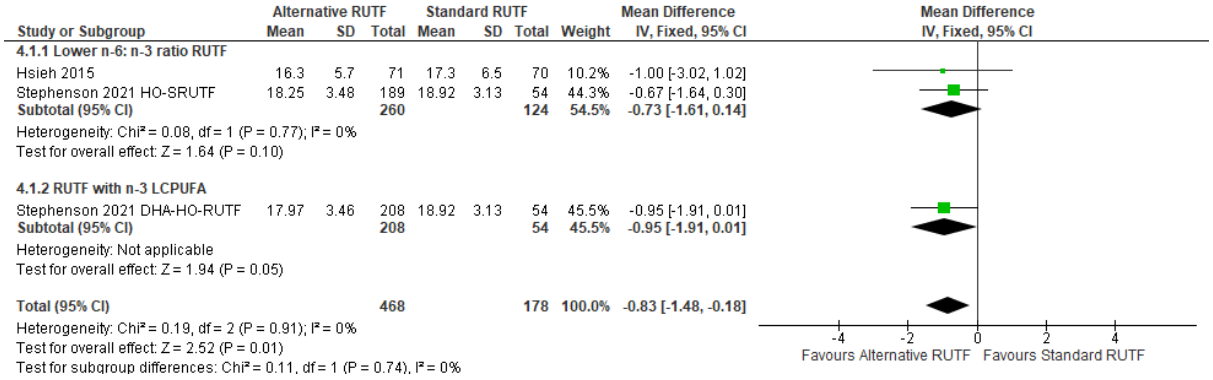
The suppliers highlighted that formulation work is needed to ensure the omega 3 powder can be incorporated into the RUTF matrix with no major organoleptic changes. They also indicated that different DHA rich powder concentrations can play a role in the organoleptic effects in RUTF. **Important to note that the impact of this change to the cost of RUTF is theoretical at this stage, the actual cost implications can be determined upon initiating work on the reformulation.**

WHO's conclusions:

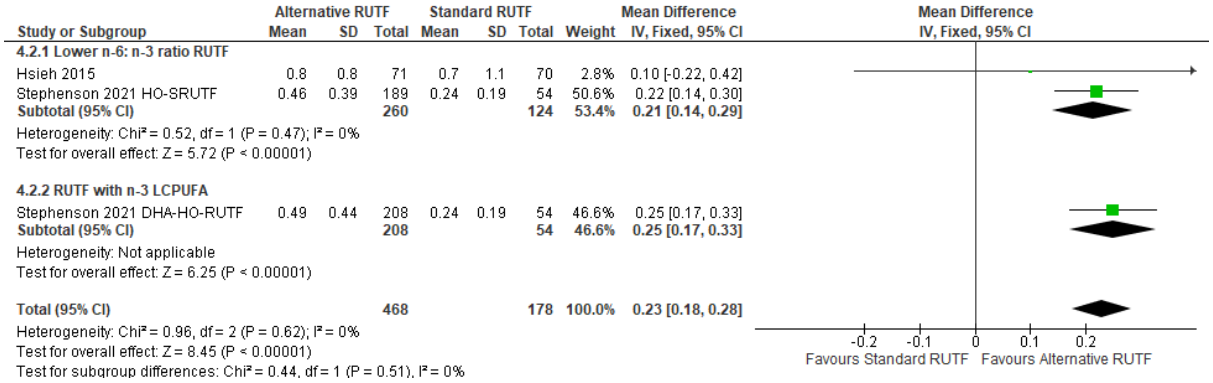
1. Adding DHA or using HO to increase ALA and lower LA content may confer some benefits to cognitive development of children recovering from severe wasting. However, the evidence is not convincing because it is only from one study. Due to limited evidence, it is not possible to establish the optimal amounts of ALA and LA in RUTF.
2. The cost implications of this change are not yet certain therefore decision-makers will need to closely monitor the cost of RUTF if this change is implemented.

ANNEXES

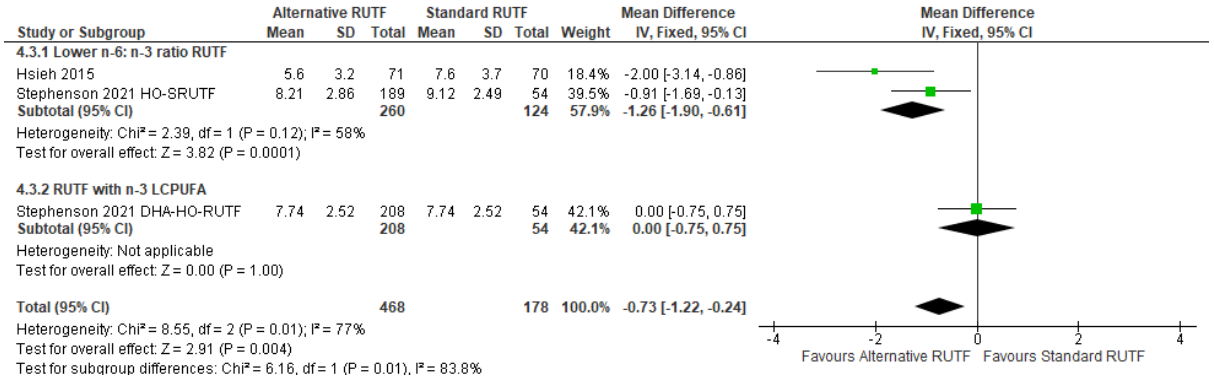
Annex 1: Effect of RUTF with altered EFA on plasma phospholipid linoleic acid composition



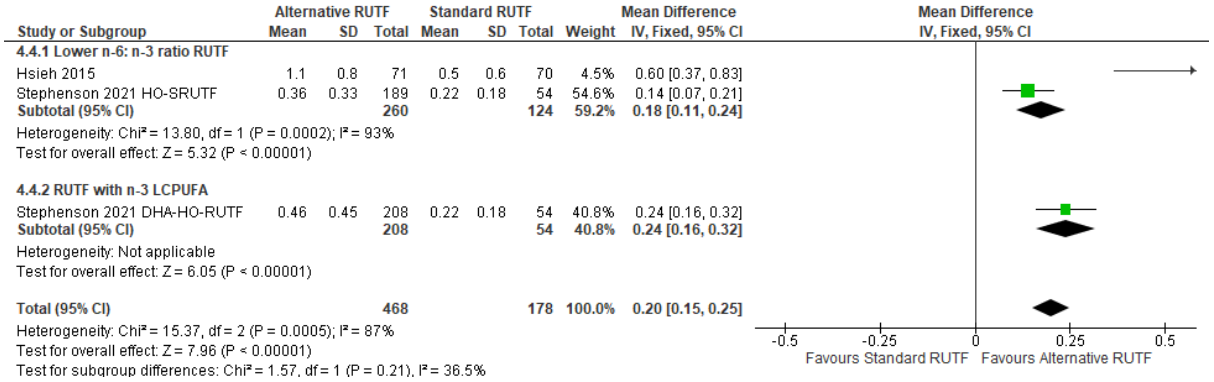
Annex 2: Effect of RUTF with altered EFA on Plasma phospholipid alpha-linolenic acid composition



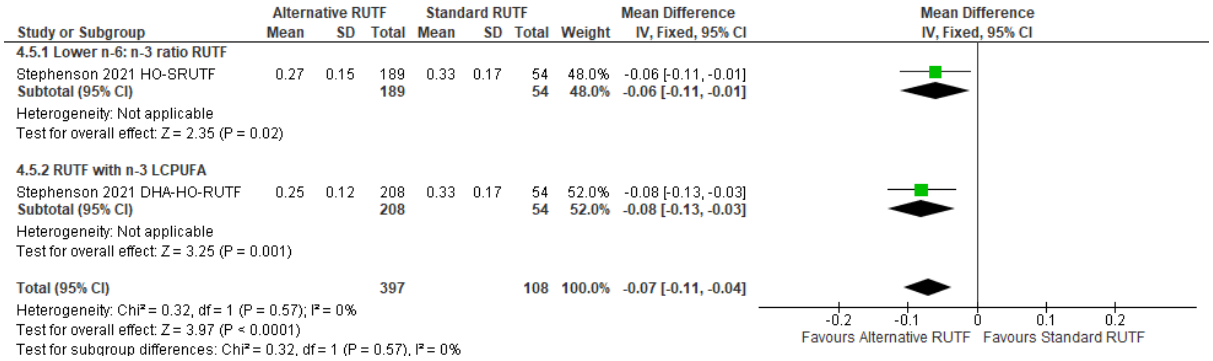
Annex 3: Effect of RUTF with altered EFA on Plasma phospholipid arachidonic acid composition



Annex 4: Effect of RUTF with altered EFA on Plasma phospholipid eicosapentaenoic acid composition



Annex 5. Effect of RUTF with altered EFA on Plasma phospholipid docosapentaenoic acid omega-6 composition



Annex 6. Effect of RUTF with altered EFA on Plasma phospholipid docosahexaenoic acid composition