An Evidence-Based Overview of PHOs and Coronary Heart Disease Risk

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International Life Sciences Institute

- Founded in 1978
- Worldwide nonprofit foundation
- Working to improve the general public’s well-being through the advancement of scientific issues related to nutrition, food safety, toxicology, risk assessment, and the environment
Prominent researchers work together to:

• Identify emerging scientific and health challenges
• Generate scientifically verifiable data
• Provide science to help harmonize policies and procedures
• Encourage scientific dialogue
ILSI Regional Branches
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  – Deena Wang, MPH

• The ILSI North America PHO Task Force
Outline of Presentation

• Background
• Project Goals
• Results and Conclusions
• Next Steps
Background - FDA Activity

On 08 November 2013, the FDA published a Federal Register notice tentatively determining that PHOs are no longer GRAS under any condition of use in food and, therefore, are food additives subject to FDA approval. [Docket No. FDA-2013-N-1317]

Rationale:

- TFA mediated changes in lipid metabolism, pro-inflammatory effects, and endothelial dysfunction lead to dose-dependent increases in CHD events in humans.
- There is no threshold intake level for industrially-produced TFA that would not increase an individual’s risk of CHD.
- Therefore, the determination is based on evidence that the consumption of PHOs (the primary source of TFAs) could be harmful under any condition of use in food.
“Expert review panels...agree that *trans* fat-mediated changes in lipid metabolism, pro-inflammatory effects, and endothelial dysfunction lead to dose-dependent increases in CHD events in humans. These *expert panels all concluded* that there is no threshold intake level for industrially-produced *trans* fat that would not increase an individual’s risk of CHD, or have adverse effects on risk factors for CHD.”
2005 Dietary Guidelines Advisory Committee Activities

• The Committee requested that the FDA Food Advisory Board address whether the scientific evidence supported a level of trans fat at 1% or less.

• A Board member concluded that:
  – “among the lower levels of trans fatty acids, the differences with respect to the increase in low density lipoprotein (LDL) cholesterol levels were not statistically distinguishable. No studies have really focused on the range of trans fatty acid intake of between zero and 3-4 percent of calories to indicate that 1 percent is more efficacious than 0.5 or 1.5 percent.”
“Although current scientific evidence does not indicate a specific acceptable daily intake for *trans* fatty acids, it is consistent with reducing *trans* fatty acid intake to a level of *less than 1% of energy* (2 g/d for a 2,000 kcal diet).”

Consume less than 10 percent of calories from saturated fatty acids and less than 300 mg/day of cholesterol, and keep *trans* fatty acid consumption *as low as possible*. 
2010 Dietary Guidelines for Americans

• Keep *trans* fatty acid consumption *as low as possible* by limiting foods that contain synthetic sources of *trans* fats, such as partially hydrogenated oils, and by limiting other solid fats.

• There is limited evidence to conclude whether synthetic and natural *trans* fatty acids differ in their metabolic effects and health outcomes.
“Expert review panels...agree that trans fat-mediated changes in lipid metabolism, pro-inflammatory effects, and endothelial dysfunction lead to dose-dependent increases in CHD events in humans. These expert panels all concluded that there is no threshold intake level for industrially-produced trans fat that would not increase an individual’s risk of CHD, or have adverse effects on risk factors for CHD.”

• Similar to SFA, there is a positive linear trend between \textit{trans} fatty acid intake and LDL-C, and therefore increased risk of CHD.

• An Upper Level is not set for \textit{trans} fatty acids because any incremental increase in \textit{trans} fatty acid intake increases CHD risk.
Evidence for Progressive, Linear Relationship

Ascherio et al. (1999) determined that a 2% increase in energy from \textit{trans} fat raised the LDL to HDL cholesterol ratio by 0.1.
Brouwer et al. (2010) cited similar findings, that for each 1% increase in energy from industrial trans fat, replacing cis-MUFAs, the LDL increased by 0.048 mmol/L.
## Intake Trends - IP-TFA (mean intakes)

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2010</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Population ≥2 y</td>
<td>2%* (4.6 g/d)</td>
<td>0.56% (1.3 g/d)</td>
<td>0.43% (1.0 g/d)</td>
</tr>
<tr>
<td>Teenage boys (13-18 y)</td>
<td>0.64% (1.8 g/d)</td>
<td>0.43% (1.1 g/d)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean IP-TFA g/p/d for Adults only

## Worst-case scenario IP-TFA intake (est.)

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Population ≥2 y</td>
<td>1.12 % (2.7 g/d)</td>
<td>.90% (2.1 g/d)</td>
</tr>
<tr>
<td>Teenage boys (13-18 y)</td>
<td>1.38% (3.9 g/d)</td>
<td>1.09 % (2.8 g/d)</td>
</tr>
</tbody>
</table>

*Doell 2012*
Evidence for Progressive, Linear Relationship

CURRENT INTAKES

Worst-Case Intakes
Request of FDA

- The FDA asked a series of questions in the *FR* notice for which they were seeking comments, with two being relevant to the proposed work:

  1. Should FDA finalize its tentative determination that PHOs are no longer GRAS?
  2. Are there data to support other possible approaches to addressing the use of PHOs in food, such as by setting a specification for *trans* fat levels in food?

Comments were due to FDA by 08 March 2014
Research Questions Remaining

• Is the relationship between PHO intake and LDL-C and HDL-C truly progressive and linear?

• Are there adequate data at low levels of exposure (<4%en) to: a) use linear regression and/or b) to assume a line through ‘0’?

• Does a threshold, above ‘0’, exist where PHO intake adversely influences lipid outcomes?
Evidence-Based Evaluation

• “Over time, the process of evaluating the totality of evidence has become more rigorous and, in recent years, more transparent. The principles of evidence-based medicine (EBM) have been adopted, in which a hierarchical approach to the evaluation of evidence is applied, with meta-analyses, systematic reviews, and randomized controlled trials (RCTs) considered the strongest types of evidence.” Maki 2014

• Examples:
  – 2009 FDA EBR System for Health Claim Evaluation
An Evidence-Based Approach to Address Research Questions

- **Aim:** To better understand and more fully delineate the risk of PHO intake at various exposures through a series of projects.

  - **Phase I:** Evidence mapping
  - **Phase II:** Dose-Response Assessment
The relationship between trans fat intake and LDL-C and HDL-C is not progressive and linear, rather, there is a threshold effect at an intake $>0\%$. 

Hypothesis (addressed by Phases I & 2)
Phase I: Evidence Mapping

Brief overview of methodology:
• An evidence map is systematic and replicable way to demonstrate information about the type and amount of research available, the characteristics of that research, and the identification of major knowledge gaps.

• Maps can be coupled with a series of summary tables, providing succinct graphical presentation of available studies to address key questions along variables of interest.

• Summary tables and evidence maps provide key information on study characteristics and study findings.

• Properly constructed summary tables:
  – Effectively convey results
  – Provide an overview of the literature in a given field
  – Enable the reader to grasp results for subsets of the literature
Phase I: Evidence Mapping

Objective: Develop an evidence map to better characterize the existing literature on industrial TFA intake at an exposure of <10% en as a substitute for functional alternatives on changes in LDL-C or HDL-C.

- And, specifically addressing the question: Are there sufficient data to perform linear regression analysis from zero, given the few data points below 3% of intake?
Search Strategy

Initial Search Criteria

- Search of PubMed (all fields) and Scopus (title, abstract, and keywords) databases (from database inception to January 14, 2014) for clinical trials, prospective cohort studies, and case-control studies

Abstrackr™ Search Strategy Schematic

**Box 1: Fatty Acids & Oils**

- Industrial Trans Fatty Acid(s)
- Industrial Produced Oil(s)
- Artifiicially Produced Oil(s)
- Partially Hydrogenated Oil(s)
- Hydrogenated Oil(s)
- Vegetable Oil (including all below)
- Corn, Olive, Canola, Sunflower, Safflower, Soybean, Rapeseed
- Trans Fat(s)
- Trans Fatty Acid(s)
- Linoleic Acid
- Conjugated Linoleic Acid(s)
- Vaccenic Acid
- Elaidic Acid
- Margarine
- Shortening
- Butter
- Palm Oil
- Palm Kernel Oil
- Animal Fat(s)
- Ruminant Fat(s)
- LDL-C
- HDL-C
- VLDL-C
- Total Cholesterol
- Triglyceride(s)
- Lipoprotein(s)
- Lipoprotein particle size
- Small/Large HDL
- Small/Large LDL
- Dyslipidemia

**Box 2: Outcomes**

Combine searches

Filter: human studies only
Filter: English studies only

~2,500 titles for abstract review
Inclusion / Exclusion Criteria

Inclusion Criteria

- Abstracts of all randomized and non-randomized clinical trials (cross-over and parallel designs), prospective cohorts studies, and case-control studies identified in the search were screened using Abstrackr™. Those that met the criteria below were included in the evidence map.

  - **Intervention/Exposure:**
    - Industrially produced oil containing TFA compared to one of the following:
      - A naturally occurring TFA
      - A predominantly monounsaturated fatty acid oil
      - A predominantly saturated fatty acid oil

  - **Outcome:**
    - LDL-C and/or HDL-C

- Articles meeting the following criteria were not included in the evidence map but collected as a bibliography:
  - Industrially produced oils containing TFA compared to a predominantly polyunsaturated fatty acid oil
  - Naturally occurring TFA (no industrially produced oils) intervention
  - Cross-sectional studies
  - Meta analyses & systematic reviews

Exclusion Criteria

- Non-English language, animal studies, In-vitro studies general reviews, addresses, bibliographies, interviews, lectures, comments, dictionary entries, editorials, or guidelines

- No TFA in intervention or TFA containing oil compared to a non-oil treatment or exposure (e.g. carbohydrate)
Results: PRIMSA Chart

Citations identified through PubMed search from Jan 14, 2014 (n=2503)

Citations accepted through Abstrackr TM screening (yes n=109) (Oil to oil n=226)

Oil to oil comparisons citations identified by experts (n=2 with TFA) (n=29 without TFA)

Articles retrieved for full text review (n=342)

Bibliographies collected
Reviews
Cross-sectional
Natural occurring TFA (comparisons)
TFA v.s. PUFA

Citations excluded (n=2161)

Eligible articles identified through Scopus search (n=2) Reference mining (n=5)

Evidence Map Phase I (n=138)

Excluded 204

RCTs (n=123)

Prospective cohort (n=8)

Case control (n=7)
Results: Numbers of Studies (by Type) Published per Year

Clinical Trials (n = 123)

Prospective Cohort Studies (n = 8)

Case-Control Studies (n = 7)

* Includes duplicate publications
Results: Clinical Trials by Oil Type

Clinical trials that met inclusion criteria  
\( n = 123 \)

- Partially hydrogenated oil  
\( n = 51 \)
  - Randomized  
    - Cross-over, \( n = 33 \)
    - Parallel, \( n = 4 \)
    - Non-randomized or not reported, \( n = 14 \)

- Non-hydrogenated industrial oil  
\( n = 31 \)
  - Randomized  
    - Cross-over, \( n = 15 \)
    - Parallel, \( n = 7 \)
    - Non-randomized or not reported, \( n = 9 \)

- TFA General  
\( n = 41 \)
  - Randomized  
    - Cross-over, \( n = 27^* \)
    - Parallel, \( n = 1 \)
    - Non-randomized or not reported, \( n = 13 \)

Includes potential publications containing duplicate data

Examples of each oil:

- **Partially hydrogenated oil**: Margarine, shortening, and oils described as “hydrogenated”
- **Non-hydrogenated industrial oil**: Most vegetable oils that did not specifically note hydrogenation (e.g. soybean, corn); cold-pressed oils were not included
- **TFA General**: Olive, palm oil, and no processing info provided

* 1 study (Mensink, et al. 1992) reported results from two separate relevant experiments in the same paper
Results: Clinical Trials Reporting TFA

Clinical trials that met inclusion criteria
n = 123

Includes potential publications containing duplicate data

Reported TFA
n = 102

Did not report TFA
n = 21

Reported TFA as % energy*
n = 58

Reported TFA as g/d**
n = 7

Reported TFA other
n = 37

Reported TFA as % of fat
n = 13

Reported TFA as g/100 g fat
n = 20

Reported TFA as % weight
n = 3

Reported TFA as g/square body meter
n = 1

Reported TFA as mol/100 mol
n = 1

*1 study (Motard-Bélanger, et al. 2008) reported TFA as g/kcal, which has used to calculate TFA as %en for the evidence map; all other studies TFA %en is reported as in the original paper;
1 study (Mensink, et al. 1992) reported results from two separate experiments in the same paper

**4 studies reported TFA as both % energy and g/d
Results:

TFA%en Distribution Among Clinical Trials

Note: TFA % energy and g/d represents actual intakes as reported in the original paper. Duplicate publications are removed.
### Number of interventions using an industrial oil and subgroup of PHO interventions

<table>
<thead>
<tr>
<th>TFA Levels</th>
<th># IP-TFA Interventions</th>
<th># PHO Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or &lt; detectable</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>&gt;0 and ≤0.5</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>&gt;0.5 and ≤1.0</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>&gt;1.0 and ≤1.5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>&gt;1.5 and ≤2.0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&gt;2.0 and ≤2.5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;2.5 and ≤3.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>
Figure 1. Results of Randomized Studies of the Effects of a Diet with Isocaloric Amounts of cis Fatty Acids (Squares) on the Ratio of LDL Cholesterol to HDL Cholesterol. The dashed line indicates the best-fit regression for trans fatty acids. The dashed line indicates the best-fit regression for trans fatty acids.
<table>
<thead>
<tr>
<th>Dose range</th>
<th>Actual dose per study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 &lt; 1.0 %en</td>
<td>0.30</td>
</tr>
<tr>
<td>1.0 &lt; 2.0 %en</td>
<td></td>
</tr>
<tr>
<td>2.0 &lt; 3.0 %en</td>
<td>2.8</td>
</tr>
<tr>
<td>3.0 &lt; 4.0 %en</td>
<td>3.00 3.50 3.60</td>
</tr>
<tr>
<td>&gt; 4.0 %en</td>
<td>4.10 6.00 6.10 7.00 7.60 8.00 8.20 10.00</td>
</tr>
</tbody>
</table>

Note: TFA % energy values presented above were estimated from Figure 1 of Ascherio, et al. 1999

<table>
<thead>
<tr>
<th>Dose range</th>
<th>Actual dose per study</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 &lt; 1.0 %en</td>
<td>0.4</td>
</tr>
<tr>
<td>1.0 &lt; 2.0 %en</td>
<td>1.9</td>
</tr>
<tr>
<td>2.0 &lt; 3.0 %en</td>
<td>2.8 2.9</td>
</tr>
<tr>
<td>3.0 &lt; 4.0 %en</td>
<td>3.0 3.2 3.6 3.6 3.8</td>
</tr>
<tr>
<td>&gt; 4.0 %en</td>
<td>4.3 5.1 5.5 5.6 5.7 5.8 5.9 6.1 6.2</td>
</tr>
<tr>
<td></td>
<td>6.2 6.6 6.8 7.1 7.3 7.6 7.6 8.2 8.3 9 10.9</td>
</tr>
</tbody>
</table>
Conclusions

• 123 studies were identified that used IP-TFA, with 102 reporting the amount of TFA consumed.
  – Of these, 58 reported TFA intake as % total energy.
  – Only 30 studies used non-hydrogenated oils or PHOs with an intervention group at <3% energy intake.

• This low number of studies is representative of the fact that the majority of the <3% energy interventions were control groups (not intervention arms), and that the source of TFA in studies with <1.5% energy were mainly non-hydrogenated oils.

• Only two studies were found in the PHO exposure range of >2.5 - ≤3% energy and these were not designed as dose response studies, but as comparisons to other oils.
Conclusions

• Despite a generous volume of literature assessing IP-TFA exposure and health outcomes:
  – limited data are available regarding low exposures.
  – Studies were not designed to address the impact of TFA intake <1%en.
  – With current mean intakes of IP-TFA at ~0.5% energy, the impact of actual exposure on risk for CHD is critical in evaluating the safety of PHO in the food supply.

• The TFA sources and dietary approaches across the studies were quite variable; therefore, combining the data from multiple studies was not warranted.

• Significant complexities exist in the available data that make cross-comparison difficult and therefore linear regression challenging: no dose-response data at 2.5 -<3% energy, use of different comparators (MUFA, PUFA and SFA), variable study duration, and confounding variables related to background diet and population disease state.
In summary, results indicate that:

- The quantity and comparability of data at low exposures of industrial TFA is not sufficient for linear regression to be used to predict a dose-response relationship at low exposure levels. Therefore, **linear regression cannot be considered an appropriate approach** to define the relationship of lipid biomarkers and exposure to PHO down to a level of zero in the diet.

- Given the quantity and type of data that are available, the use of dose-response **modeling is not only feasible, but necessary**, to determine the safety of PHO exposure with regard to LDL and HDL.
Feasibility of Modeling

- The available data are extensive, and while problematic in several regards, particularly at low exposures, *these data are sufficient for modeling purposes*.

- A better understanding of several of the *Modes of Action* (MOAs) for CHD, or at least for a change in LDL due to PHO, *is needed before determining whether a threshold for an increase in LDL-C is likely*, or not, in the dose scale for industrially-produced TFA.

- Modeling available data would assist in this determination, and may provide the basis for a projection of risk at all points in the dose scale, rather than default to a linear, or some other, empirical function.
Feasibility of Modeling

• In the docket, it is suggested that TFA-mediated changes in lipid metabolism, pro-inflammatory effects, and endothelial dysfunction might lead to dose-dependent increases in CHD in humans. It is important to note that many other factors, such as other chemicals, microorganisms, changes in diet, exercise regimens, nutritional status and obesity can all impact CHD as well. Modeling the available data would assist in determining those factors most likely to be associated with various types of CHD. This evaluation will help with future research focusing on these factors as well.

• A brief look at the work of Brouwer et al. suggests a linear trend for industrial TFA, but the data for ruminant TFA are decidedly not linear, and in fact might be hormetic. An explanation for this difference can best be approached through an understanding of MOA, for which models are a useful supporting tool.
Next Steps: Phase II-Dose-Response Modeling

• Three elements:
  1. Establish biological understanding of threshold (MOA determination)
  2. Meta-regression to determine shape of dose-response curve
  3. Identify safe dose of PHO through point of departure determination
Research Needs

- Clinical (LDL-C) and public health significance (CHD) of a 0.5%en reduction in IP-TFA - especially when considering replacement nutrients

- Updated assessment of TFA intakes from all sources
Thank you!
TFA Codings: Partially Hydrogenated Oils (PHO)

- Hydrogenated oil, Partially hydrogenated oil (soybean oil, sunflower oil)
- Lightly hydrogenated soybean oil
- PMS Blends 1 & 2 (poly/mono/sat fat veg oils partially hydrogenated
- PHFO, partially hydrogenated fish oil,
- Shortening
- Margarine, Hard margarine, Squeeze margarine, Soft margarine, Tub margarine, Semiliquid margarine, Dietetic margarine, Corn oil margarine, TFA-margarine, TFA-enriched margarine, Trans-margarine, Low sat fat FA margarine
- Soybean oil-based traditional stick margarine
- Oil + margarine
- Sunflower-enriched margarine
- Low erucic rape seed oil margarine
- Margarine with PUFA, Fish oil-enriched margarine
- Palm margarine, High palm margarine
- McGregor’s margarine
- SAFA margarine, high-SAFA margarine
TFA Codings: Industrial non-PHO

- Corn oil
- Canola oil/Rapeseed oil
- Sunflower oil, Sunflower seed oil
- Safflower oil
- Soybean
- Vegetable oil
- High-oleic soybean oil, High-oleic acid with soybean oil
- Gold’n canola
- High oleic sunflower oil
TFA Codings: TFA General

- Trans fats no specified, Trans fatty acids not specified
- High TFA, Total TFA, Moderate TFA
- Industrial TFA, TFA from industrially produced sources
- Elaidic acid, Elaidic acid fat blends
- Olive oil (type unknown)
- Palm oil (type unknown)
- Palm kernel oil (type unknown)
- Coconut oil (type unknown)
- Canola, corn, olive & rice bran oil
- Olive oil + sunflower oil
- High oleic, low trans diet
- Canola + TFA
- Trans MUFA, MUFA (with TFA amt documented)
- Trans 18:1
- High trans fat diet, TFA-enriched diet, High linoleic diet (with TFA amt documented)
- High trans soybean oil
- 50:50 palm and high oleic sunflower oil, Mix of palm & high oleic sunflower oil
- Unhydrogenated soybean oil
Comparison Oil Tags

**MUFA/SFA/PUFA**
- Linoleic, Oleate
- EV Olive oil, palm, stearin (mix)
- TFA-free canola
- Mono cis blend, palm, oleic

**PUFA**
- SDA, Stearidonic acid
- N6 PUFA
- N3 PUFA
- Linolenic acid
- Linoleic acid

**SFA**
- Saturated fat diet, High sat fat diet
- SFA, Saturated fatty acids, Sat Fat
- Stearate, stearic acid
- Palmitic acid, Lauric, myristic
- LMP, Lauric-Myristic-Palmitic acid mixture
- Extra virgin palm oil, Extra virgin palm kernel oil
- Extra virgin coconut oil

**MUFA**
- MUFA, monounsaturated fatty acids
- Monounsaturated fatty acid diet
- High oleic fatty acid diet, oleic rich diet
- Oleic fatty acids
- Extra virgin olive oil, Virgin Olive oil
- CMUFA, High cis MUFA
# Comparison Oil Tags

## Naturally occurring TFA
- TFA from natural, TFA from natural sources
- Conjugated linoleic acid, CLA
- rTFA, High rTFA, Moderate rTFA, Low rTFA butter
- Butter & Hard cooking fat, Solid fat, Butter, Lard
- Dairy or ruminant (e.g. lipids in milk/cheese), Dairy fat, Cow’s milk,
- Milk fat, Modified milk, Beef, Beef Tallow
- Cocoa butter, Peanut
- SAFA diet (mostly butter)
- Vaccenic acid, Vaccenic acid enriched diet
- Very low fat diet

## Mixture (unknown)
- Butter & vegetable oil mix
- Habitual butter, palm, canola
- Habitual diet, Control diet, Baseline diet,
- Butter, olive oil blend, Butter, sunflower oil blend

## Other
- TFA + SFA, TFA + Stearic
- No TFA
## Change in Plasma TFA concentrations: NHANES 2000 to 2009

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccenic acid</td>
<td>56</td>
</tr>
<tr>
<td>Elaidic acid</td>
<td>63</td>
</tr>
<tr>
<td>Palmitelaidic acid</td>
<td>49</td>
</tr>
<tr>
<td>Linoelaidic acid</td>
<td>49</td>
</tr>
<tr>
<td>Sum of trans-fatty acids</td>
<td>58</td>
</tr>
</tbody>
</table>

*Vesper HW, Kuiper HC, Mirel LB, Johnson CL, Pirkle JL. JAMA. 2012;307:562-563*
Results: Age and Sex Distribution Among RCT Publications Reporting TFA as %en

**Age (y)**

<table>
<thead>
<tr>
<th>Age (y)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>22.0</td>
</tr>
<tr>
<td>25% Percentile</td>
<td>27.6</td>
</tr>
<tr>
<td>Median</td>
<td>31.85</td>
</tr>
<tr>
<td>75% Percentile</td>
<td>62.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>100.0</td>
</tr>
<tr>
<td>Mean</td>
<td>41.3</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>17.8</td>
</tr>
<tr>
<td>Std. Error</td>
<td>2.5</td>
</tr>
<tr>
<td>Lower 95% CI of mean</td>
<td>36.4</td>
</tr>
<tr>
<td>Upper 95% CI of mean</td>
<td>46.3</td>
</tr>
</tbody>
</table>

*5 studies that reported TFA as % energy did not report mean age

**Females (%)**

<table>
<thead>
<tr>
<th>Females (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>0.0</td>
</tr>
<tr>
<td>25% Percentile</td>
<td>49.0</td>
</tr>
<tr>
<td>Median</td>
<td>59.0</td>
</tr>
<tr>
<td>75% Percentile</td>
<td>87.5</td>
</tr>
<tr>
<td>Maximum</td>
<td>100.0</td>
</tr>
<tr>
<td>Mean</td>
<td>57.4</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>33.1</td>
</tr>
<tr>
<td>Std. Error</td>
<td>4.4</td>
</tr>
<tr>
<td>Lower 95% CI of mean</td>
<td>48.6</td>
</tr>
<tr>
<td>Upper 95% CI of mean</td>
<td>66.2</td>
</tr>
</tbody>
</table>

*1 study that reported TFA as % energy did not report the sex of study participants

* Includes duplicate publications
Results:
Number of Studies by Oil/Fat Type and Subject Health Status in RCT Publications

* Includes duplicate publications
Results: TFA Distribution Among Clinical Trials using Partially Hydrogenated Oil(s)

Distribution of TFA (% energy) in studies using PHOs

<table>
<thead>
<tr>
<th>TFA (%en) Bin Center</th>
<th># of treatment arms</th>
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Actual TFA intake < 4.0% energy per study treatment arm

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<tr>
<th>TFA (%en)</th>
<th>0.09</th>
<th>0.2</th>
<th>0.23</th>
<th>0.8</th>
<th>0.8</th>
<th>0.91</th>
<th>0.91</th>
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<tbody>
<tr>
<td>0 &lt; 1.0% en</td>
<td>0.09</td>
<td>0.2</td>
<td>0.23</td>
<td>0.8</td>
<td>0.8</td>
<td>0.91</td>
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<td>1.0 &lt; 2.0% en</td>
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<td>1.85</td>
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<td>2.0 &lt; 3.0% en</td>
<td>3.19</td>
<td>3.3</td>
<td>3.3</td>
<td>3.7</td>
<td>3.9</td>
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<tr>
<td>3.0 &lt; 4.0% en</td>
<td>3.19</td>
<td>3.3</td>
<td>3.3</td>
<td>3.7</td>
<td>3.9</td>
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Note: TFA % energy represents actual intakes of each intervention arm as reported in the original paper. Duplicate publications are removed.
Search Strategy

Manual bibliography search of the following:

- Dietary Fats: Total Fats and Fatty Acids chapter in the *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients).*

Method Quality Check

- A random subset of citations (n = 250) identified by the broad search criteria were duplicate screened using the Abstrackr™ software to assess and revise screening strategy.
- Decisions regarding screening inclusion/exclusion were based on the review of one individual as the duplicate screening resulted in 97.2% agreement (243 out of 250 abstracts).
  - If questions arose during screening, an independent second reviewer was consulted.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Brouwer et al, 2010</th>
<th>Ascherio et al, 1999</th>
<th>Mozaffarian &amp; Clark, 2009</th>
<th>Mensink et al, 2008</th>
<th>Possible Dose-Response for low level intakes*</th>
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</table>

Studies were included if there were at least 3 treatment arms and at least 1 of the treatment arms provided an IP-TFA at <3.0%en