### Processing Steps affecting contaminants

<table>
<thead>
<tr>
<th>Processing Aids</th>
<th>CO1 Process Steps affecting contaminants</th>
<th>RBD Process Steps affecting contaminants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutralization</td>
<td>Acidification</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>Ethanol, Sodium Hydroxide, RO water</td>
<td>Sulfuric Acid or Citric Acid Solution</td>
</tr>
<tr>
<td>Retention Time, mins</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>Aflatoxin</td>
<td>50:50 Water: Oil Fractionation</td>
<td>50:50 Water: Oil Fractionation</td>
</tr>
<tr>
<td>Deoxynivalenol (DON)</td>
<td>100:0 Water: Oil Fractionation</td>
<td>100:0 Water: Oil Fractionation</td>
</tr>
<tr>
<td>Penicillin</td>
<td>100:0 Water: Oil Fractionation</td>
<td>100:0 Water: Oil Fractionation</td>
</tr>
<tr>
<td>Tylosin</td>
<td>100:0 Water: Oil Fractionation</td>
<td>100:0 Water: Oil Fractionation</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>100:0 Water: Oil Fractionation</td>
<td>100:0 Water: Oil Fractionation</td>
</tr>
</tbody>
</table>

### Physical and chemical properties

#### Mycotoxins

<table>
<thead>
<tr>
<th>Temperature</th>
<th>pH condition</th>
<th>Water (mg/L at 25°C)</th>
<th>Ethanol (mg/L at 25°C)</th>
<th>Adsorption Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxin</td>
<td>25°C or above</td>
<td>Unstable &gt;250°C</td>
<td>Unstable &gt;2pH</td>
<td>233-994</td>
</tr>
<tr>
<td>Deoxynivalenol (DON)</td>
<td>150°C</td>
<td>Unstable &gt;150°C</td>
<td>Unstable &gt;10pH</td>
<td>5600</td>
</tr>
<tr>
<td>Penicillin</td>
<td>35°C or above</td>
<td>Unstable &gt;35°C</td>
<td>Unstable &gt;3pH</td>
<td>18704</td>
</tr>
<tr>
<td>Tylosin</td>
<td>100°C or above</td>
<td>Inactivated &gt;100°C</td>
<td>Inactivated &gt;3pH and &gt;9pH</td>
<td>5000</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>100°C or above</td>
<td>Inactivated &gt;100°C</td>
<td>Inactivated &gt;2pH</td>
<td>231</td>
</tr>
</tbody>
</table>

#### Antibiotics

<table>
<thead>
<tr>
<th>Temperature</th>
<th>pH condition</th>
<th>Water (mg/L at 25°C)</th>
<th>Ethanol (mg/L at 25°C)</th>
<th>Adsorption Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginiamycin</td>
<td>100°C</td>
<td>Inactivated &gt;100°C</td>
<td>Inactivated &gt;3pH and &gt;9pH</td>
<td>5000</td>
</tr>
<tr>
<td>Penicillin</td>
<td>35°C or above</td>
<td>Inactivated &gt;35°C</td>
<td>Inactivated &gt;3pH and &gt;9pH</td>
<td>18704</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>100°C or above</td>
<td>Inactivated &gt;100°C</td>
<td>Inactivated &gt;2pH</td>
<td>231</td>
</tr>
</tbody>
</table>

Low water solubility: ≤10 mg/l
Moderate water solubility: 10-1,000 mg/l
High water solubility: >1,000 mg/l
Solubility Literature Cited:

**Virginiamycin**


**Penicillin**


David J. Maggs, Chapter 3 - Ocular Pharmacology and Therapeutics, Stato’s Fundamentals of Veterinary Ophthalmology (Fourth Edition), 2008


**Erythromycin**


**Tylosin**


**Tetracyclin**


**Aflatoxin**


Fumonisin


**DON**

Impact of food processing and identification treatments on mycotoxin contamination, Karlovsky, Sumar, Barbillier, Moester, Eisenbrand, Perrie, Oswald, Speijers, Chisolm, Recker, Dussert; Mycotoxin Res (2016) 32:179–205

https://www.tocris.com/products/deoxynivalenol_39760d_data_sheets
Stability Literature Cited

Virginiamycin Islam, Toledo, Hamdy, Stability of virginiamycin and penicillin during alcohol fermentation, Biomass and Bioenergy 17 (1999) 369-376

Penicillin Islam, Toledo, Hamdy, Stability of virginiamycin and penicillin during alcohol fermentation, Biomass and Bioenergy 17 (1999) 369-376

Erythromycin Fiese, Steffen, Comparison of the acid stability of azithromycin and erythromycin


Fumonisin Jafar Milania and Gisoo Malekib, Effects of processing on mycotoxin stability in cereals, J Sci Food Agric 2014; 94: 2372–2375

## Processing Steps

<table>
<thead>
<tr>
<th>Process</th>
<th>Antigen</th>
<th>Antibody</th>
<th>Antibiotic</th>
<th>Temperature, °F</th>
<th>Time, mins</th>
<th>Solubility (mg/L @ 25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaOH solution – 8 w%</td>
</tr>
<tr>
<td>Drying</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Water 0.5%</td>
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<tr>
<td>Oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethanol, water</td>
</tr>
<tr>
<td>Separation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Citric Acid</td>
</tr>
<tr>
<td>Degumming</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaOH solution – 8 w%</td>
</tr>
<tr>
<td>Water Wash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Water 0.5%</td>
</tr>
<tr>
<td>Bleaching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethanol, water</td>
</tr>
<tr>
<td>Winterization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Citric Acid</td>
</tr>
</tbody>
</table>

## Thermo-physical Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
</tr>
<tr>
<td>Mass Fractionation</td>
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</tr>
<tr>
<td>Solubility</td>
<td></td>
</tr>
<tr>
<td>Fraction</td>
<td></td>
</tr>
<tr>
<td>State</td>
<td></td>
</tr>
<tr>
<td>Vaporize</td>
<td></td>
</tr>
<tr>
<td>Effect</td>
<td></td>
</tr>
</tbody>
</table>

## Decomposition

- Fumonisin
- Erythromycin
- Tetracycline
- Citric Acid

## Unstable
- Fumonisin
- Erythromycin
Toxicology Questions

Q1. Please provide details about the original literature search strategy, such as the search terms and the timeframe (month/year to month/year), and please update the literature search to include the most recent possible references.

Response:

Literature searches were conducted in April 2020 using PubMed, with supplemental searches performed in GoogleScholar to identify studies containing information pertinent to the safety of corn oil. The following search terms were used with the search field restricted to titles, and with no other limitations:

Corn oil OR 8001-30-7 OR corn oils OR oil, corn OR maize oil OR maize oils OR oil, maize OR oils, maize OR lipomul

Titles of 882 citations were returned and reviewed, followed by review of abstracts in cases where the title did not provide sufficient information to judge the relevance of a publication. Based on this initial titles and abstracts review, a large number of citations were not safety relevant and were excluded from further review. Publications that were excluded from further consideration were:

- Mechanistic studies, in vitro, mode of action, and mixture studies (258, e.g. gene expression, protein expression, and biochemical pathway analyses; experimentation on genetically modified animals; evaluations on additive, synergistic, or antagonistic effects; initiation and promotion effects involving other compounds, such as carcinogens)
- Behavioral studies (18, e.g. reinforcement behavior, palatability, food preference, orosensory, feeding motivation, conditioning, and grooming)
- Agriculture, animal feed, and non-relevant mammalian species studies (122)
- Composition, chemical properties, analytical methods/techniques, and technical applications (322)
- Pre-clinical toxicity studies using non-relevant routes of exposure (4, e.g. subcutaneous, percutaneous and intraperitoneal routes of exposure)
- Efficacy studies (25)
- Dated publications (pre-1980, reviews, and commentaries (81))
- Unrelated articles (28, e.g. environmental-related study, social science, study concerns a compound/substance that is not relevant to corn oil)

All pre-clinical studies related to ADME and toxicity and clinical studies and case reports (potentially containing safety outcomes reporting) were retained for further review. A total of 24 citations were determined to be potentially relevant and the full publications (3 with abstracts...
only) were obtained and screened for information related to the toxicity and ADME of corn oil. The publications were categorized according to the primary physiological, toxicological, and/or biochemical effects that were observed, including ADME, cardiac effects; liver, kidney, pancreas, GI effects; lipid and metabolic effects; DART; and cancer. The citations for these publications are summarized in Table 1. Additional literature search was conducted for ADME publications and is described in response to question 3 (below).

Table 1. Safety Relevant Citations

<table>
<thead>
<tr>
<th>Types of Effect</th>
<th>Author, year</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, kidney</td>
<td>Milin et al., 2000</td>
<td>Milin C, Domitrović R, Tota M, Giacometti J, Cuk M, Radošević Stasić B, Ciganj Z. Effect of olive oil- and corn...</td>
</tr>
<tr>
<td>Types of Effect</td>
<td>Author, year</td>
<td>Citation</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>DART</td>
<td>Guerra et al., 2019</td>
<td>Guerra LHA, Tamarindo GH, de Campos SGP, Taboga SR, Vilamaior PSL. Do mineral and corn oil serve as potential...</td>
</tr>
<tr>
<td>Types of Effect</td>
<td>Author, year</td>
<td>Citation</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
</tbody>
</table>
Q2. Further, FDA’s literature search revealed reports of adverse effects from orally administered corn oil on the following organs/systems or physiological effects associated with the dysregulation of these organs/systems in rodents (rats or mice); some examples are listed below:

I. **Kidney**, such as proximal tubular as well as glomerular lesions.
II. **Pancreas**, such as hyperplasia of acinar cells of the exocrine pancreas.
III. **Heart**, such as cardiac fibrosis, myocardial damage.
IV. **Metabolic effects**, such as insulin resistance and type 2 diabetes.
V. **Maternal effects**, such as abnormal clinical signs after parturition, reduced pup viability.

Please address why chronic consumption of COZ corn oil wouldn’t be associated with adverse effect(s) as described in the published references.

Response:

Findings in the literature searches as described under Q1 are summarized below. For all of the responses provided to Q2, the dose conversion is based on the following reference: EFSA Scientific Committee; Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579. [32 pp.] doi:10.2903/j.efsa.2012.2579.

Cardiac effects

Three studies that were identified from the literature search containing cardiovascular-related endpoints are summarized in Table 2. Each study describes a single dose of corn oil that was administered to rats in the diet. Eid et al. (2019a,b) showed that rats fed a high-fat diet enriched in corn oil (HFD-CO, 40% fat; equivalent to 36 g/kg bw/day\(^1\)) for 8 weeks exhibited traits of type 2 diabetes, along with increased left ventricular collagen synthesis; disrupted systolic and diastolic function; and increased oxidative stress, cell death activation, and ultrastructural changes. In a study comparing diets fortified with 15% (w/w; weight ratio of rat chow to oil is 100:15; equivalent to 7.5 g/kg bw/day\(^2\)) of either fresh, once-heated, five-times heated, or ten-times heated corn oil administered to rats in the diet for 16 weeks, the overall results showed that all of the heated oils caused a significant increase in blood pressure (Das et al., 2017).

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\(^1\) 40% high fat diet-corn oil was converted to 40 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 400,000 mg/kg diet = 40%; 1 mg/kg in rat feed for a subchronic duration study is equivalent to 0.09 mg/kg bw/day; therefore, 400,000 mg/kg diet is equivalent to 36 g/kg bw/day (i.e. (400,000 X 0.09)/1000).

\(^2\) 15% w/w of corn oil was converted to 7.5 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 150,000 mg/kg diet = 15%; 1 mg/kg in rat feed for a chronic duration study is equivalent to 0.050 mg/kg bw/day; therefore, 150,000 mg/kg diet is equivalent to 7.5 g/kg bw/day (i.e. (150,000 X 0.050)/1000).
Collectively, these studies demonstrate that repeated, subchronic exposure to dietary corn oil in very high amount $\geq 7.5$ g/kg bw/day in rats can adversely affect cardiac ultrastructure and function as well as induce traits consistent with type 2 diabetes.

### Table 2. Studies with cardiac effects in rats

<table>
<thead>
<tr>
<th>Reference</th>
<th>Relevant endpoint(s) specific to corn oil</th>
<th>Primary results/conclusion specific to corn oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eid et al., 2019a</td>
<td>Left ventricular (LV) fibrosis was evaluated in rats fed a low-fat diet or high-fat diet enriched in corn oil (HFD-CO, 40% fat; equivalent to 36 g/kg bw/day$^1$) for 8 weeks</td>
<td>HFD-CO induced type 2 diabetes phenotype and increased LV collagen synthesis in rats that were fed a HFD-CO (40% fat) diet.</td>
</tr>
<tr>
<td>Eid et al., 2019b</td>
<td>Atrial cells ultrastructure, antioxidant levels and markers of intrinsic cell death in adult male Wistar healthy control and T1DM-induced rats fed control or HFD-CO (40% fat; equivalent to 36 g/kg bw/day$^1$) for 60 days</td>
<td>Healthy rats that received a HFD-CO (40% fat) displayed T2DM phenotype; systolic and diastolic function were impeded; increased oxidative stress, cell death activation, and ultrastructural changes</td>
</tr>
<tr>
<td>Das et al., 2017</td>
<td>Blood pressure changes in male Sprague-Dawley rats (200-280 g in body weight) that were fed control diet, or basal diet fortified with 15% (w/w; weight ratio of rat chow to oil is 100:15; equivalent dose 7.5 g/kg bw/day$^2$) of either fresh, once-heated, five-times heated, or ten-times heated corn oil for 16 weeks</td>
<td>Significant increase in the blood pressure in groups fed the basal diet with 7.5 g/kg bw/day of once-heated, five- and ten-times heated corn oil compared to the control diet; overall results suggest that repeatedly heated corn oil increases blood pressure and vascular inflammation</td>
</tr>
</tbody>
</table>

### Liver, Kidney, Pancreas and GI Effects

Six studies that were identified from the literature search containing liver, kidney, pancreas, or gastrointestinal (GI) effects are summarized in Table 3. Two separate, 21-day, single dose dietary studies are described whereby mice and rats were fed corn oil at 5% (w/w; equivalent to 10 g/kg bw/day$^3$) and 12% in the diet, respectively (Milin et al., 2000; Nwanguma et al., 1998). Compared to mice that received a control diet, corn oil-exposed mice had increases in spleen iron and calcium concentrations, liver and thymus calcium. Rats that were fed corn oil (12% in the

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$^1$ 5% w/w corn oil was converted to 10 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 50,000 mg/kg diet = 5%; 1 mg/kg in mouse feed for a subacute duration study is equivalent to 0.2 mg/kg bw/day; therefore, 50,000 mg/kg diet is equivalent to 0.2 g/kg bw/day (i.e. (50,000 X 0.2)/1000).
diet; equivalent to 14.4 g/kg bw/day\(^4\)) exhibited significantly increased liver and kidney lipid peroxides, decreased body weight gains, and increased relative liver weights compared to controls. In a separate dietary study from Alexander et al. (1987; abstract only) in weanling rats that received diets containing 15% (by weight; equivalent to 18 g/kg bw/day\(^5\)) of fresh or laboratory-heated corn oil (FCO, HCO), total weight gain, feed consumption, feed efficiency, liver and kidney weights were increased in FOC-exposed rats, while in HCO-exposed rats, reported clinical signs included diarrhea, dermatitis, seborrhea, and hair loss as well as thymus and liver injury.

In a gavage study, female Sprague-Dawley rats were administered 0, 2, or 10 ml corn oil/kg body weight/day (equivalent to 0, 1.8, or 9 g/kg bw/day, respectively, based on the corn oil density of 0.9 g/ml) via gavage during pre-mating (2 weeks), mating, gestation, and until day 3 of lactation (Sato et al., 2000). Overall results showed that the kidneys of dams fed an animal protein diet combined with corn oil providing intake of 9 g/kg bw/day of corn oil had severe lesions in the proximal tubular epithelium, which was reported as necrosis and fatty degeneration (Sato et al., 2000). The study authors concluded that the animal protein diet may have enhanced the corn oil toxicity (Sato et al., 2000). In a separate oral gavage study in male Fischer-344 rats that were administered 5 ml/kg bw/day corn oil (equivalent to 4.5 g/kg bw/day based on the corn oil density of 0.9 g/ml) for 5 weeks (5 days/week), results revealed small intestinal mucosal tissue mass, and increased DNA and protein content, along with increased DNA/dry mass ratio that was suggestive of rapid cell division (Anderson, 1987). Finally, Eustis and Boorman (1985) reviewed pancreata data from corn oil vehicle control and untreated control F344/N male rats in 37, 2-year carcinogenicity studies to assess the extent and strength of the association of proliferative exocrine pancreatic lesions with corn oil gavage. The study authors concluded that “there was no relationship between incidences of proliferative acinar lesions and the animal laboratory, the animal source, and the brand, lot, or peroxide level of the corn oil. The incidences of focal acinar hyperplasia and acinar adenoma were related to maximum mean body weights attained by the groups during the course of the study.”

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\(^4\) 12% w/w of corn oil was converted to 14.4 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 120,000 mg/kg diet = 12%; 1 mg/kg in rat feed for a subacute duration study is equivalent to 0.12 mg/kg bw/day; therefore, 120,000 mg/kg diet is equivalent to 14.4 g/kg bw/day (i.e. (120,000 X 0.12)/1000).

\(^5\) 15% w/w of corn oil was converted to 18 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 150,000 mg/kg diet = 15%; 1 mg/kg in weanling rat feed is equivalent to 0.12 mg/kg bw/day; therefore, 150,000 mg/kg diet is equivalent to 18 g/kg bw/day (i.e. (150,000 X 0.12)/1000).
Taken together, corn oil administered in the diet and via gavage at doses ranging from 4.5 -18 g/kg bw/day have been shown to cause adverse effects in the liver, kidney, and GI, while pancreatic effects observed in rat 2-yr carcinogenicity studies are not attributed to corn oil.

Table 3. Studies with liver, kidney, pancreas, GI effects in rats and mice

<table>
<thead>
<tr>
<th>Reference</th>
<th>Relevant endpoint(s) specific to corn oil</th>
<th>Primary results/conclusion specific to corn oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milin et al., 2000</td>
<td>Mineral content changes in the liver, spleen, and thymus were examined in male Balb/c mice (2-3 mo old) that were fed diets enriched with 5% corn oil added to the standard pellet diet, w/w (equivalent to 10 g/kg bw/day) for 21 days</td>
<td>Compared to the control diet, diet enriched with corn oil (5%) caused an increase in spleen iron and calcium concentrations; increased liver calcium; and increased thymus calcium</td>
</tr>
<tr>
<td>Sato et al., 2000</td>
<td>Kidney histopath evaluations in female Sprague-Dawley rats divided into two (CA-1 and CE-2) groups* that were administered 0, 2, or 10 ml corn oil/kg body weight/day (equivalent to 0, 1.8 or 9 g/kg bw/day, respectively) via oral gavage during pre-mating (2 wk), mating, gestation, and until day 3 of lactation</td>
<td>Kidneys of dams fed the CA-1 diet combined with 9 g/kg bw/day of corn oil exhibited severe lesions in the proximal tubular epithelium reported as necrosis and fatty degeneration; CA-1 diet was suggested to enhance the corn oil toxicity</td>
</tr>
<tr>
<td>Nwanguma et al., 1998</td>
<td>Tissue levels of lipid peroxides in organs, organ and body weights of male Wistar albino rats that were administered thermally oxidized corn oil (12% fat in the diet; equivalent to 14.4 g/kg bw/day) in the diet for 21 days</td>
<td>At the 14.4 g/kg bw/day dose, significantly increased lipid peroxides were observed in the liver and kidney; body weight gains were significantly decreased; relative liver weights were significantly increased compared to controls</td>
</tr>
<tr>
<td>Anderson, 1987</td>
<td>Intestinal responses in male Fischer-344 rats that were administered 5 ml/kg bw/day corn oil (equivalent to 4.5 g/kg bw/day) via oral gavage for 5 weeks (5 days/week)</td>
<td>At the 4.5 g/kg bw/day dose, small intestinal mucosal tissue mass, DNA and protein content were increased along with increased DNA/dry mass ratio that was suggestive of rapid cell division</td>
</tr>
<tr>
<td>Alexander et al., 1987</td>
<td>Organ, tissue, and biochemical effects were evaluated in 5 groups of male weanling rats that received diets containing 15% (by weight; equivalent to 18 g/kg bw/day) of FCO-exposed rats (18 g/kg bw/day corn oil), total weight gain, feed consumption, feed efficiency, liver and kidney weights were increased.</td>
<td>In FCO-exposed rats (18 g/kg bw/day corn oil), total weight gain, feed consumption, feed efficiency, liver and kidney weights were increased.</td>
</tr>
</tbody>
</table>
### Metabolic Effects

Five studies that were identified from the literature search containing lipid and metabolic effects are summarized in Table 4. Recent single-dose dietary studies performed in mice that received 32% (w/w; equivalent to 64 g/kg bw/day\(^6\)) corn oil for 8 weeks (Pavlisova et al., 2016) or 19% (w/w; equivalent to 38 g/kg bw/day\(^7\)) corn oil for 6 weeks (Wong et al., 2015) revealed that corn oil-exposed mice gained weight, had impaired insulin sensitivity, decreased locomotor activity, lower respiratory ratio, hyperinsulinemia, and impaired glucose disposal. These results suggest that repeated exposure to dietary corn oil at high doses in mice can cause metabolic impairment.

In a separate dietary study from Deshaies (1986; abstract only), rats fed diets high in corn oil (65% of calories as sucrose or corn oil, equivalent to 58.5 g/kg bw/day\(^8\)) for 4 weeks had higher HDL to total cholesterol ratio compared to rats that consumed sucrose; plasma total triglyceride levels were also 73% higher in the sucrose-treated animals compared to corn oil. Corn oil-

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\(^6\) 32% w/w corn oil was converted to 64 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 320,000 mg/kg diet = 5%; 1 mg/kg in mouse feed for a subchronic duration study is equivalent to 0.2 mg/kg bw/day; therefore, 320,000 mg/kg diet is equivalent to 64 g/kg bw/day (i.e. (320,000 X 0.2)/1000).

\(^7\) 19% w/w corn oil was converted to 38 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 190,000 mg/kg diet = 19%; 1 mg/kg in mouse feed for a subchronic duration study is equivalent to 0.2 mg/kg bw/day; therefore, 28,500 mg/kg diet is equivalent to 38 g/kg bw/day (i.e. (190,000 X 0.2)/1000).

\(^8\) 65% corn oil in the diet was converted to 58.5 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 650,000 mg/kg diet = 65%; 1 mg/kg in rat feed for a subchronic duration study is equivalent to 0.09 mg/kg bw/day; therefore, 650,000 mg/kg diet is equivalent to 58.5 g/kg bw/day (i.e. (650,000 X 0.09)/1000).
treated rats accumulated large amounts of liver triglycerides; however, due to limited study details, the implications for this finding are unclear. Boyle et al. (1996; abstract only) concluded that corn oil is inappropriate for use in infant formulas based on large changes in liver long-chain polyunsaturated fatty acid profiles. Lastly, Apgar et al. (1987) determined that rats fed up 0, 5, 10, or 20% (equivalent to 0, 6, 12, or 24 g/kg bw/day, respectively) corn oil in the diet for 2 weeks had an overall fecal fatty acid profile of 27-34% palmitic acid (16:0), 22-32% stearic acid (18:0) and 25-37% oleic acid (18:1).

Collectively, these studies reveal that repeated dietary corn oil exposure at high doses ranging from 28.5 – 58.5 g/kg bw/day in rats and mice leads to phenotypes associated with metabolic dysfunction.

**Table 4. Studies with lipid and metabolic effects in rats and mice**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Relevant endpoint(s) specific to corn oil</th>
<th>Primary results/conclusion specific to corn oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pavlisova et al., 2016</td>
<td>Male C57BL/6N mice fed a corn oil (32% w/w; equivalent to 64 g/kg bw/day) diet for 8 weeks</td>
<td>At the 64 g/kg bw/day dose, weight gain induction and impaired insulin sensitivity were observed</td>
</tr>
<tr>
<td>Wong et al., 2015</td>
<td>Estimation of spontaneous locomotor activity, body composition and in vivo metabolic outcomes in female C57/Bl6 mice fed either high-fat (HF) diets [40% energy corn oil (CO; 19% w/w; equivalent to 38 g/kg bw/day) or isocaloric olive oil (OO; 19% w/w) or chow for 6 weeks</td>
<td>Mice fed a HF diet containing 38 g/kg bw/day of corn oil demonstrated reduced spontaneous locomotor activity, lower respiratory ratio, hyperinsulinemia and impaired glucose disposal; skeletal muscle failed to up-regulate fat oxidation genes, indicating metabolic insufficiencies</td>
</tr>
<tr>
<td>Boyle et al., 1996</td>
<td>Omega 3 long-chain polyunsaturated fatty acid (LCP) accretion in red blood cells, liver, and brain phospholipids were evaluated in rats fed diets containing infant formula fat blends with essential fatty acids provided from soy and/or corn oil.</td>
<td>Large changes in liver LCP profiles; substantial tissues differences b/w the oils (no further details provided in the abstract); authors state that corn oil is inappropriate for use in infant formulas</td>
</tr>
<tr>
<td>Apgar et al., 1987</td>
<td>Study to evaluate fecal fatty acid profile and fecal lipid elimination in male Sprague-Dawley rats fed 0, 5,</td>
<td>Overall fecal fatty acid profiles in rats fed up to 24 g/kg bw/day corn oil diets consisted primarily of 27-34% palmitic</td>
</tr>
</tbody>
</table>

---

9 5, 10, and 20% corn oil in the diet was converted to 6, 12, and 24 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 50,000, 100,000, 200,000 mg/kg diet = 5, 10, and 20%, respectively; 1 mg/kg in rat feed for a subacute duration study is equivalent to 0.12 mg/kg bw/day; therefore, 50,000, 100,000, 200,000 mg/kg diet is equivalent to 6, 12, and 24 g/kg bw/day, respectively (e.g. (50,000 X 0.12)/1000).
GRN 000890 – Responses to Toxicology Questions (April 24, 2020)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Relevant endpoint(s) specific to corn oil</th>
<th>Primary results/conclusion specific to corn oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deshaies, 1986 (abstract only)</td>
<td>Plasma lipoprotein lipid composition and white adipose tissue lipoprotein lipase activity in rats fed diets high in either sucrose or corn oil (65% of calories as sucrose or corn oil, equivalent to 58.5 g/kg bw/day) for 4 weeks; reference diet group was also included</td>
<td>HDL to total cholesterol ratio was higher in the animals fed 58.5 g/kg bw/day corn oil compared to the sucrose-treated group, which had 73% higher plasma total triglyceride levels compared to the corn oil group; oil-fed rats accumulated large amounts of liver triglycerides; however, due to limited study details, the implications for this finding are unclear</td>
</tr>
</tbody>
</table>

**DART-related effects**

Three studies that were identified from the literature search containing DART-related effects are summarized in Table 5. In a single-dose study, Guerra et al. (2019) evaluated the effects of corn oil on the prostate of male Mongolian gerbils that received corn oil at 0.1 ml/day (equivalent to 1.286 g/kg bw/day, based on the corn oil density of 0.9 g/ml and the reported average animal weight of 70 g) via gavage for 25 days. Overall results from the study showed reduced body weight, an increased incidence of atrophic acini, decreased epithelial and stromal androgen receptor as well as increased epithelial levels of ERalpha and ERbeta. In another single-dose study, Moral et al. (2011) showed that female Sprague-Dawley rats fed a high corn oil (20% corn oil w/w, equivalent to 20 g/kg bw/day) diet from weaning through puberty exhibited increased body weight around puberty, increased corpora lutea, and earlier sexual maturation compared to low-fat diet fed animals.

In a separate dietary study, female Sprague-Dawley rats were administered 0, 2, or 10 ml corn oil/kg body weight/day (equivalent to 0, 1.8, or 9 g/kg bw/day, respectively, based on the corn oil density of 0.9 g/ml) via oral gavage during pre-mating (2 weeks), mating, gestation, and until day 3 of lactation (Sato et al., 2000). No effects on mating or fertility indices were reported and no clinical signs observed during gestation. However, at the highest tested dose of 9 g/kg bw/day, decreased food consumption and decreased body weight gain from lactation days 0-4 (only when combined with an animal protein diet) were observed. Additionally, mortality and

---

10% 20% corn oil in the diet was converted to 18 g/kg bw/day based on EFSA guidelines (2012): 1 mg/kg diet = 0.0001%; 200,000 mg/kg diet = 20%; 1 mg/kg in rat feed for a subchronic duration study is equivalent to 0.09 mg/kg bw/day; therefore, 200,000 mg/kg diet is equivalent to 18 g/kg bw/day (i.e. (200,000 X 0.09)/1000).
clinical signs were observed post-parturition as well as reduced pup viability when combined with an animal protein diet. Thus, adverse effects from corn oil were primarily observed when combined with an animal protein diet.

Taken together, these studies reveal differential effects of corn oil exposure in Mongolian gerbils and rats based on the corn oil dosage and route of administration. In male Mongolian gerbils that were administered 1.286 g/kg bw/day of corn oil via gavage for 25 days, body weights were decreased and effects on the prostate were observed. Separately, in female rats that received 0, 1.8, or 9 g/kg bw/day of corn oil via gavage combined with an animal protein diet during pre-mating (2 wk), mating, gestation, and until day 3 of lactation, rats from the highest dose group had decreased body weight, mortality, exhibited clinical signs, and reduced pup viability; however, the study authors note these observed effects occurred when combined with an animal protein diet. In a separate non-gavage rat study, females that that received an 18 g/kg bw/day high corn oil diet from weaning through puberty exhibited earlier sexual maturation and increased body weight. Although the Sato et al. (2000) study is the only multiple-dose study among the three that were identified for DART, the dose range is inadequate for determining dose-dependent effects. The collective data from the three studies suggest reproductive toxicity below 1.286 g/kg bw/day based on the effects that were observed in male Mongolian gerbils, and developmental toxicity at less than 18 g/kg bw/day based on the observed effects in female Sprague-Dawley rats fed an 18 g/kg bw/day corn oil diet from weaning through puberty.

Table 5. Studies with DART effects

<table>
<thead>
<tr>
<th>Reference</th>
<th>Relevant endpoint(s) specific to corn oil</th>
<th>Primary results/conclusion specific to corn oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guerra et al., 2019</td>
<td>Effects of corn oil on the prostate were evaluated in male Mongolian gerbils that received corn oil at 0.1 ml/day (equivalent to 1.286 g/kg bw/day, based on the corn oil density of 0.9 g/ml and the reported average animal weight of 70 g) via oral gavage for 25 days</td>
<td>At a dose of 1.286 g/kg bw/day of corn oil, the following were observed: atrophic acini, reduced body weight, decreased androgen receptor in the epithelium and stroma, and increased epithelial levels of ERalpha and ERbeta</td>
</tr>
<tr>
<td>Moral et al., 2011</td>
<td>Effects of a high corn oil diet (20% corn oil w/w, equivalent to 18 g/kg bw/day) on puberty and mammary gland development in female Sprague-Dawley rats fed high corn oil diet from weaning through puberty</td>
<td>At a corn oil dose of 18 g/kg bw/day, increased body weight nearing puberty, increased corpora lutea, and earlier sexual maturation were observed compared to low-fat diet fed animals</td>
</tr>
<tr>
<td>Sato et al., 2000</td>
<td>Corn oil effects on gestation, parturition, and lactation in female Sprague-Dawley rats divided into 2 (CA-1 and CE-2) groups* that were administered 0, 2, or 10 ml corn</td>
<td>-No effects on mating or fertility indices; No clinical signs observed during gestation Effects observed at the highest tested dose of 9 g/kg bw/day:</td>
</tr>
</tbody>
</table>
Cancer Effects

Three studies that were identified containing cancer-related information along with an NTP study are summarized in Table 6. In the NTP study, control male rats that received a corn oil vehicle were shown to have a higher incidence of pancreatic proliferative lesions and a lower incidence of mononuclear cell leukemia compared to untreated control males (NTP, 1994). Additionally, corn oil is not mutagenic in Salmonella typhimurium strains TA97, TA98, TA100, or TA1535, with or without S9 (NTP, 1994). Based on a study comparing the effects of various concentrations of safflower (very high in polyunsaturated fat), corn oil (high levels of polyunsaturated and monounsaturated fats), and tricaprylin (high in saturated medium-chain fatty acids) (tricaprylin) on the incidence and pattern of neoplasms in the F344/N rat, it was concluded that safflower oil and tricaprylin do not offer significant advantages over corn oil as a gavage vehicle in long-term rodent studies (NTP, 1994).

The primary objective of each of the remaining three studies was to comprehensively evaluate corn oil gavage data obtained from carcinogenicity studies in order to determine tumor incidence. Overall conclusions from the study authors are in general agreement with the NTP (1994) regarding the higher incidence of pancreatic proliferative lesions and a lower incidence of mononuclear cell leukemia in corn oil vehicle-treated control male rats compared to untreated control males. The study authors further suggest that the pancreatic acinar cell tumor incidence is due to a combination of fat intake and body weight (Rao and Haseman, 1993).

Table 6. Studies on cancer in rats and mice

<table>
<thead>
<tr>
<th>Reference</th>
<th>Relevant endpoint(s) specific to corn oil</th>
<th>Primary results/conclusion specific to corn oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTP, 1994</td>
<td>Studies conducted to evaluate the effects of various concentrations of safflower oil, corn oil, and tricaprylin on the incidence and pattern of neoplasms in the F344/N rat; safflower oil and</td>
<td>Corn oil-treated, control male rats exhibited a higher incidence of pancreatic proliferative lesions and a lower incidence of mononuclear cell leukemia compared to untreated control males</td>
</tr>
</tbody>
</table>
### Relevant endpoint(s) specific to corn oil

- Tricaprylin were also evaluated as replacements for the corn oil vehicle.

### Primary results/conclusion specific to corn oil

- Corn oil was not determined to be mutagenic in Salmonella typhimurium strains TA97, TA98, TA100, or TA1535, +/- S9
- Safflower oil and tricaprylin do not offer significant advantages over corn oil as a gavage vehicle in long-term rodent studies

#### Rao and Haseman, 1993

<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary of the influence of corn oil gavage and different nonpurified diets on spontaneous tumor incidences in 64 dietary groups and 59 corn oil gavage control groups in 2-yr studies on ~6100 Fischer 344 rats of each sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Corn oil gavage significantly increased the body weight and pancreatic tumor incidences but decreased the incidence of leukemia, which resulted in higher survival in male rats.</td>
</tr>
<tr>
<td></td>
<td>Corn oil gavage significantly lowered the body weight and anterior pituitary tumor incidence in female rats.</td>
</tr>
<tr>
<td></td>
<td>Pancreatic acinar cell tumor incidence was suggested by the study authors to be due to a combination of fat intake and body weight.</td>
</tr>
</tbody>
</table>

#### Haseman and Rao, 1992

<table>
<thead>
<tr>
<th>Reference</th>
<th>Survival, body weight, and site-specific tumor rates in untreated, corn oil gavage, and water gavage control Fischer 344 (F344/N) rats from 88 National Toxicology Program (NTP) long term carcinogenicity studies were evaluated to determine which factors were primarily responsible for inter-study variability.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Corn oil increases pancreatic acinar cell tumor rates and reduces leukemia rates in male F344/N rats but has no significant effect on tumors in female rats.</td>
</tr>
<tr>
<td></td>
<td>Corn oil increases body weight and survival in male rats.</td>
</tr>
<tr>
<td></td>
<td>The gavage technique per se does not appear to affect tumor rates.</td>
</tr>
</tbody>
</table>

#### Haseman et al., 1985

<table>
<thead>
<tr>
<th>Reference</th>
<th>Control data on F344/N rats and (CS7BL/6N X C3H/HeN)F1 (B6C3F1) mammary tumor virus-free mice from the NTP were evaluated to compare tumor incidence between untreated controls versus animals that were administered corn oil via gavage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Corn oil-treated male F344/N control rats showed a higher incidence of pancreatic acinar cell adenoma and a lower incidence of leukemia (primarily mononuclear cell leukemia) than did the corresponding untreated controls.</td>
</tr>
<tr>
<td></td>
<td>The increased incidences of pancreatic acinar cell adenoma observed in corn oil-treated male rats were associated with elevated body weights compared to untreated controls.</td>
</tr>
<tr>
<td></td>
<td>Female F344 rats and male and female B6C3F1 mice showed little or no evidence of a difference in tumor incidence between corn oil gavage-treated and untreated controls.</td>
</tr>
<tr>
<td></td>
<td>A review of ~300 carcinogenesis studies conducted by the National Cancer Institute (NCI) and the NTP revealed that there were no corn oil gavage studies in which</td>
</tr>
</tbody>
</table>
### Reference Relevant endpoint(s) specific to corn oil

<table>
<thead>
<tr>
<th>Reference</th>
<th>Relevant endpoint(s) specific to corn oil</th>
<th>Primary results/conclusion specific to corn oil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Increased incidences of pancreatic acinar cell tumors or leukemia in male F344/N rats were the sole evidence of the carcinogenicity of a test chemical.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corn oil appears to have little impact on the interpretation of NCI-NTP carcinogenicity studies</td>
</tr>
</tbody>
</table>

Overall, the pre-clinical evidence showed that exposure to very high amount of corn oil could result in various target organ effects, including:

- Subchronic dietary exposure corn oil in amount $\geq 7.5$ g/kg bw/day in rats can adversely affect cardiac ultrastructure and function as well as induce traits consistent with type 2 diabetes.
- Corn oil administered in the diet and via gavage at doses ranging from 4.5 -18 g/kg bw/day have been shown to cause adverse effects in the liver, kidney, and GI; however, pancreatic effects observed in rat 2-yr carcinogenicity studies are not attributed to corn oil.
- Repeated dietary corn oil exposure at high doses ranging from 28.5 – 58.5 g/kg bw/day in rats and mice leads to phenotypes associated with metabolic dysfunction.
- The collective data from DART studies suggest reproductive toxicity below 1.286 g/kg bw/day, and developmental toxicity at less than 18 g/kg bw/day

Assuming a default 60 kg body weight, these effects were observed with very high intake in the range of 77 g to 3,516 g of corn oil per day. These intakes are much higher than the EDI of 6 g of corn oil per day based on US consumption data (see appendix H of GRN). Corn oil is a food with a long history of use in the U.S. food supply. The principal food uses of corn oil include salad and cooking oil, margarine, blends of butter, mayonnaise and emulsion type salad dressings. Corn oil is used as an oil ingredient in a variety of packaged and restaurant foods, including spaghetti sauce, potato chips and snack foods, French fries and breaded foods, baking mixtures, frosting and whipped toppings, crumb coating for meat and poultry, and baked goods. The published literature also indicates that corn oil was commonly used in infant formulas in the U.S. as recently as the late 1990s (LSRO, 1998; Ponder et al. 1992; Green Corkins and

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12 Ponder DL, Innis SM, Benson JD, Siegman JS. Docosahexaenoic acid status of term infants fed breast milk or infant formula containing soy oil or corn oil. Pediatr Res. 1992 Dec;32(6):683-8
Shurley, 2016\textsuperscript{13}). Further, due to its beneficial effect of significantly lowering elevated blood pressure, a qualified health claim petition – Corn Oil and Corn Oil-Containing Products and a Reduced Risk of Heart Diseases (Docket No. 2006P-0243) was filed and FDA concluded that there is sufficient scientific support for a qualified health claim for corn oil (FDA, 2007\textsuperscript{14}). Thus, chronic consumption of COZ corn oil, which is the same as conventional edible corn oil, would not be expected to be associated with the effects observed in animals at very high doses that well exceed dietary exposure to corn oil among the US population.

**Q3.** Please discuss what is known about the absorption, distribution, metabolism and excretion (ADME) profile of corn oil, which informs the safety of COZ corn oil.

**Response:**

Literature searches were conducted in April 2020 using PubMed, with supplemental searches performed in GoogleScholar to identify studies containing information related to the pharmacokinetics (i.e. absorption, distribution, metabolism, and excretion; ADME) of corn oil. The following search terms were used with the search field restricted to titles, and with no other limitations:

Corn oil OR 8001-30-7 OR corn oils OR oil, corn OR maize oil OR maize oils OR oil, maize OR oils, maize OR lipomul AND (metabolism OR metabolic OR absorption OR bioavailability OR pharmacokinetics OR oral OR pharmacodynamics)

Titles of 73 citations were returned and reviewed, followed by review of abstracts in cases where the title did not provide sufficient information to judge the relevance of a publication. Based on this initial titles and abstracts review, only a single study was identified that contained relevant information on the pharmacokinetics of corn oil. Although this single study is limited in scope, it was included for comprehensiveness. Publications that were excluded from further consideration were:

- Mechanistic studies, mode of action, mixture studies, studies on an unrelated compound (44, e.g. biochemical pathway analyses; evaluations on additive, synergistic, or antagonistic effects; initiation and promotion effects involving other compounds, such as carcinogens)
- Behavioral grooming study (1)


\textsuperscript{14} Food and Drug Administration (FDA). Qualified Health Claims: Letter of Enforcement Discretion – Corn Oil and Corn Oil- Containing Products and a Reduced Risk of Heart Disease (Docket No. 2006P-0243). March 25, 2007.
- Agriculture, animal feed, and non-relevant mammalian species studies (7)
- Chemical properties, analytical methods/techniques, and technical applications (6)
- Dated publications (pre-1980 with no available abstract (13))
- A study from Pavlisova et al., 2016 that was previously captured for lipid and metabolic effects that is described in Table 4

Two studies that were not captured in the 73 citations from the ADME literature search but were identified in the first literature search (i.e. 882 citations) as well as five separate reviews were included for supporting information.

**Relevant ADME Citations:**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Citation</th>
</tr>
</thead>
</table>

**Corn oil ADME**

Corn oil is a highly digestible fat that consists of approximately 60%, 25%, and 15% polyunsaturated, monosaturated, and saturated fatty acids, respectively (Apgar et al., 1987;
Mitchell et al., 1989; Dupont, 1990; Patterson et al., 2012; Wang and White, 2019; Barrera-Arellano, 2019). Therefore, the metabolism and bioavailability of corn oil is expected to be similar to other fatty acids. Following dietary ingestion of fats such as corn oil, the fatty acids are hydrolyzed by pancreatic enzymes and bile salts prior to being absorbed in the small intestine, for eventual distribution to other tissues in the body such as the liver and adipose (Lichtenstein et al., 2012). In the single study that was captured from the ADME literature search, male rats that received an intragastric bolus dose of corn oil comprised of 82.4% oleic and linoleic acids had a peak absorption of 2.0 ± 0.4 mL/h (Degrace et al., 1996). The study authors concluded that intestinal absorption of fatty acids such as corn oil can vary based on fatty acid composition, but the metabolic processes underlying fatty acid metabolism are generally the same (Degrace et al., 1996). Thus, the pharmacokinetic profile of corn oil can be reasonably inferred from the processes underlying fatty acid metabolism.

Q4. In Table 7 on Page 28, the units of the percentage values presented in columns 5 (FCC Specification) and 6 (COZ Corn Oil Mean) are not specified. Please address whether these values reflect a percentage of 100 g oil (as in column 2) or a percentage of 100 g fatty acids (as in column 3).

Response:

The percentage values in column 5 (FCC Specification) reflects a percentage of 100 g oil. The percentage in column 6 (COZ Corn Oil Mean) reflects a percentage of 100 g oil.

Q5. Please clearly state in your own words your OVERALL CONCLUSION that the COZ corn oil (subject of this GRAS notice) is GRAS for its intended use and why the concerns associated with corn oil exposure raised by various studies such as these noted above by FDA are adequately addressed.

Response:

COZ corn oil derived from distillers corn oil by CO1™ and conventional RBD processes is equivalent to conventional corn oil. COZ corn oil meets FCC specifications for color, water, free fatty acids, iodine value, peroxide value, unsaponifiable matter, and fatty acids. In addition to having a fatty acid profile consistent with conventional corn oil, the phytosterol and fat soluble vitamin concentrations are comparable to conventional corn oil. COZ corn oil therefore is nutritionally equivalent to conventional corn oil. The proposed use of COZ corn oil as edible corn oil will be substitutional to other conventional corn oil sources in the US market. As shown in the response to Q2, the dietary exposure to corn oil in the US is well below intake level in animal studies in which adverse effects were observed. Conventional corn oil has had a long history of dietary exposure with recognized health benefits via an approved qualified health
claim. Conventional corn oil is generally recognized as safe (GRAS). As such, COZ corn oil, which is the same as conventional edible corn oil, is also GRAS.
Chemistry questions

Manufacturing and Raw Materials

Q1. In Tables 3 and 4 on pages 17 and 18, you have listed several processing aids and materials with “regulatory status”. Some of them do not address the uses described in your notice. For clarity, please provide a statement that any processing aids, materials and components added during manufacture, and any antioxidants added to the final product are commonly used in production of edible oils, food grade, and safe and suitable for their intended use.

Response:
All processing aids used in the CO1™ processing steps have regulatory approvals for use in food, are commonly used in the production of edible oils, and are safe and suitable for their intended use.

Q2. Please provide a statement that the COZ corn oil is produced in accordance with current good manufacturing practices and general requirements for production of human food (21 CFR Part 110).

Response:
Production of COZ corn oil is comprised of two distinct phases, as described in the GRN document. Both production processes are in compliance with current good manufacturing practices and general requirements for production of human food.

Q3. On page 14, the notice states that several components added during ethanol production and fermentation byproducts may be present in the crude oil.

a. Please provide a narrative based on standard industry practices to address removal of the other chemicals (i.e. urea, caustic soda, oil recovery chemicals, enzymes, and pH control agents) and fermentation byproducts that may be present following crude oil production.

Response:
As shown in Appendix C, Table D1, urea, caustic soda, sulfuric acid, enzymes, yeast used in the fermentation process have regulatory approval for use in food. Except for PhibroBreak Corn Oil additive, all substances listed in Table D2 are used for the purpose of boiler and water treatment in the ethanol production process. The active ingredients used in these substances are listed as permissible chemicals as boiler water additives and are listed in 21 CFR 173.310. As a result, these substances are designed to be highly soluble in water and will be separated into the aqueous streams of the fermentation process. In an unlikely scenario where residues of these substances are present in the crude corn oil feedstock, they will be removed in the neutralization step of the Phase 1 CO1 process and refining step of the Phase II RBD process due to their high solubility in water.

PhibroBreak is a processing aid for the separation of crude corn oil from condensed solubles at ethanol production facilities. A major component of this substance is a polymeric surfactant the use of which is GRAS in feed. Further, the manufacturer provided a letter stating that the additive does

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not pose any health risk to humans. Most of the substance will remain in the rag layer; an extremely low amount of it might be left as a residue in the crude corn oil. Any residue will be removed by the filtration process step during dewaxing in the Phase 1 CO1 process and bleaching in the Phase II RBD process.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Active Ingredient</th>
<th>GRAS status of active Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>A VOxOUT 70C CO2 Scrubber Chemical</td>
<td>Ammonium Bisulfite4</td>
<td>Extremely Soluble in water</td>
</tr>
<tr>
<td>B Boiler MP Plus Scale Inhibitor Boiler Chemical</td>
<td>Sodium Hydroxide5</td>
<td>Extremely Soluble in water. 21 CFR 184.1763 Sodium hydroxide</td>
</tr>
<tr>
<td>C BWT 200 B Alkalinity Builder Boiler Chemical</td>
<td>Sodium or Potassium Hydroxide is typically used</td>
<td>Extremely Soluble in water. 21 CFR 184.1763 Sodium hydroxide</td>
</tr>
<tr>
<td>D Oxigon 200 Oxygen Scavenger Boiler Chemical</td>
<td>Inorganic sulfite, diethyhydroxylamine are typically used. 6</td>
<td>Extremely soluble in water</td>
</tr>
<tr>
<td>E RLT 19 Condensate Treatment Boiler Chemical</td>
<td>Amines such as 2-Diethyldimethanol are typically used. 7</td>
<td>Extremely soluble in water</td>
</tr>
<tr>
<td>F Bulab 8170GR Evaporator Anti-scalant</td>
<td>Poly acrylic acids, Polyphosphates, Phosphonates are typically used. 8</td>
<td>Extremely soluble in water</td>
</tr>
<tr>
<td>G FermaSure XL</td>
<td>Chlorine Dioxide9</td>
<td>Extremely Soluble in water. 21 CFR 173.300</td>
</tr>
<tr>
<td>K Phibro AC Clean-in-Place Chemical</td>
<td>Nitric Acid, Proprietary Chemical10</td>
<td>Extremely Soluble in water. 49 CFR 173.158</td>
</tr>
</tbody>
</table>

b. Please clarify whether active enzymes and red yeast used in ethanol production are expected to remain in the refined oil.

Response:
As shown in Appendix C, Table D1 of the GRN, the enzymes and yeast used in the ethanol production have regulatory approval to be used in the production of food. In addition, due to the amount of water used in the fermentation process, the enzymes and the red yeast used in the ethanol production must be either soluble or dispersible in water. The likelihood of enzymes and yeast residues being present in the crude oil is very low. In the event any of the residues are present in the crude oil, they will be removed in the dewaxing filters during the dewaxing step of the Phase 1 CO1 process.

Q4, In Table D-2 on page 62, the notice lists substances A through L that you state, “do not have

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2 Letters from the manufacturer stating that the additive does not pose human health risk (attached to this response)
3 PhibroBreak SDS sheet (attached to this response)
4 VOxOUT SDS sheet (attached to this response)
5 Boiler MP Plus SDS Sheet (attached to this response)
8 https://www.sciencedirect.com/topics/engineering/antiscalant
9 FermaSure XL SDS sheet (attached to this response)
10 Phibro AC SDS sheet (attached to this response)
GRN 000890 – Responses to Chemistry Questions (April 24, 2020)

the appropriate regulatory status.” Please provide additional information to assess the regulatory status of these substances. Consider the following in your response:

a. Please provide a statement addressing if the substances A through K are standard to the corn oil industry or industrial fermentations for food use.
   Please see response above in Q3-a

b. Substance L is added directly to the crude oil and therefore would not meet the “food contact substance” definition as you have cited. Please address its regulatory status as a direct ingredient.
   Please see response above in Q3-a

c. You have provided a Threshold of Toxicological Concern (TTC) discussion for substances termed “impurities” (p. 35-39, 61-62). We note that FDA has a process for submitting a threshold of regulation (TOR) exemption, and information provided in a GRAS notice cannot serve as a TOR exemption submission. Further, we note that boiler water additives are within the purview of the Division of Food Contact Substances (DFCS) within OFAS, while sanitation chemicals may be within the purview of DFCS or the Environmental Protection Agency. We would not evaluate safety of these materials within the context of a GRAS notice.

Response:
None of the substances in question are being treated as food contact substances for which TOR can be used. Rather, the substances are being treated as residues the safety of which are being addressed through the threshold of toxicological concern (TTC) paradigm. TTC is based on scientific risk assessment principles and can be used to assess the safety of such residues. The lowest TTC value (0.15 microgram/day) was used as the basis to derive an acceptable limit.
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Antibiotics Use

The notice suggests that the assurance that antibiotics are not present in COZ corn oil relies on two factors: 1) absence of antibiotics in the crude oil (as determined by monthly random sampling (regular protocol), and 2) removal of any residual antibiotics during the method of manufacture. The information provided in the notice does not sufficiently address this topic. We request that you address the following:

Q1. Antibiotic use in ethanol production varies by country. Please clarify whether the source of the crude corn oil is only domestic or also from outside the U.S. If crude corn oil is obtained from outside the U.S., please specify where it is obtained from.

Response:
Only domestic crude oil is used as feedstock.

Q2. On page 15, the notice cites a report by the U. S. Grain Council that states that the following antibiotics may be used in production of ethanol from distiller’s grains: virginiamycin, erythromycin, penicillin G, tetracycline, and tylosin.

a. Will suppliers of crude corn oil provide data on use of antibiotics other than those five?

Response:
Yes, the suppliers of crude corn oil will provide data on use of antibiotics other than those five

b. If so, what are the acceptance criteria for crude corn oil for antibiotics other than those five?

Response:
Similar to the five antibiotics, the acceptance criteria for the remaining antibiotics will be ‘Not Detected (LOD=0.05ppm)’.

Q3. Please comment whether the FDA LIB (4438) method for analysis of antibiotic residues is validated for use in an oil matrix.

Response:
The method was validated for oil matrices. The method is based on FDA LIB 4438. While the extraction procedure is the same, the method uses a different analytical column, mobile phases, and gradient.

Q4. Have specifications been set for limits on the levels of antibiotics in the refined oil product? Please discuss.

Response:
Antibiotics are not expected to be present in the crude oil starting material and that will be verified using methods with low limits of detection. Therefore, antibiotics will not be present in the refined oil.

Q5. Please provide a narrative to explain why antibiotics will not remain in the crude oil after
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fermentation, and how the RBD process (pp. 18-19, pp. 66-68) would remove residual antibiotics. Consider the following in your response:

a. Include reference(s) used for the data in Appendix E (pp. 66-68).
   Response: please see comprehensive narrative response below; references have been added to the updated Appendix E (enclosed with this response in excel format to facilitate viewing)

b. Consider relevant publications regarding distribution of antibiotic residues between distiller’s grains (dry matter) and crude oil.
   Response: please see comprehensive narrative response below

c. The information in the tables pp. 66-68 suggests at least a portion of the antibiotics might distribute in oil. Please clarify how the information in this table was used to predict the distribution of antibiotics in water:oil (100:0) to support statements regarding removal of antibiotics during degumming and neutralization (pp. 18-19). Support your assumption with data on fractionation of antibiotics in these matrices (either from DDGS producer data or in a laboratory setting).
   Response: Information in the narrative (see below) and updated Appendix E addresses the above question.
   Water solubility of a contaminants is measured in mg/l. Solubility is divided into three categories as below11:
   Low water solubility: <10 mg/l
   Moderate water solubility: 10-1,000 mg/l
   High water solubility: >1,000 mg/l
   Based on the above criteria, the antibiotics and mycotoxins are predicted to be distributed in the solvent (water and ethanol) in various ratios.
   Low water solubility: 25:75 Water: Oil
   Moderate water solubility: 50:50 Water: Oil
   High water solubility: 100:0 Water: Oil

d. Several cells in the Tables pp. 66-68 are blank. Please rectify.
   Response: Appendix E has been updated to reflect parameters used in the mass balance calculation; extraneous data not relied upon have been removed to avoid confusion. The updated Appendix E is enclosed with this response in excel format to facilitate viewing

Response Narrative:
During the corn fermentation process, antibiotics are typically added to minimize bacterial contamination that could result in lower ethanol yield and quality. Virginiamycin and Penicillin are the most widely used antibiotics in the corn fermentation process.12 FDA’s Center for Veterinary Medicine (CVM) conducted a nationwide survey in 2012 for 13 possible antibiotic residues in Distillers Grains. The survey found that out of total 46 samples analyzed, only 3 samples had

11 Ronald Ney, "Fate and Transport of Organic Chemicals in the Environment" 1995; p. 10
detectable concentrations of erythromycin, penicillin and/or virginiamycin.\textsuperscript{13} The first sample contained 0.58 ppm erythromycin, the second sample contained 0.24 ppm penicillin and 0.15 ppm virginiamycin, and the third sample contained 0.16 ppm virginiamycin. Erythromycin had a detection limit of 0.5 ppm, penicillin had a detection limit of 1.0 ppm, and virginiamycin had a detection limit of 0.1 ppm.\textsuperscript{14}

**Virginiamycin M1:** Virginiamycin is a commonly used antibiotic in corn fermentation process added at levels of 0.25 ppm to 2ppm. Virginiamycin is approved by the FDA to be used in treatment of livestock, for example at levels of 5.5 to 110 ppm in swine feed. In November 1993, the FDA’s Center for Veterinary Medicine issued a “letter of no objection” for the use of virginiamycin at concentrations of between 2 to 6 ppm in the fermentation phase of ethanol and distiller’s dried grain with solubles? (DDGS) production, and had no objection to potential virginiamycin residues of 0.2 to 0.5 ppm in DDGS. Virginiamycin concentrations below 0.5 ppm pose no concern to animals consuming the feed, nor to humans consuming food derived from those animals.\textsuperscript{15, 16} The FDA also conducted a quantitative risk assessment on virginiamycin and human health in 2004 and concluded that virginiamycin poses no threat to human health.\textsuperscript{12, 16} Virginiamycin is significantly inactivated at temperatures of the ethanol distillation process at 100°C.\textsuperscript{17} Temperature conditions in the drying step in Phase I CO1 process and deodorization step in the Phase II RBD process can be as high as 260°C - enough to deactivate any Virginiamycin residues if present in the crude corn oil. Virginiamycin has limited solubility in both water (45mg/l)\textsuperscript{18} but high solubility in polar organic solvents such as ethanol.\textsuperscript{19, 20} Aqueous ethanol solutions are used as solvent in the neutralization step of Phase I CO1 process. So, any residues of Virginiamycin that might be present in crude corn oil will be removed in the process.

**Penicillin G:** Penicillin is often added at concentrations above 1.5 mg/L in fuel ethanol production due to the possibility of induced enzymatic degradation of the antibiotic. This concentration is much lower than concentrations approved for use in food animals.\textsuperscript{12} The stability of penicillin is directly affected by temperature and pH. High temperatures (>35°C) and pH values greater than 8.0 and less than 4.0 cause penicillin to become unstable.\textsuperscript{21} It was reported that within 48 hours, penicillin G (0.5 unit/mL) was almost completely inactivated at 35°C and at pH of 3.8, 4.0, 4.2, and 4.5 during sterile malt glucose yeast extract fermentation.\textsuperscript{22}

\textsuperscript{13} FY 2010 Nationwide Survey of Distillers Grains for Antibiotic Residues, 2009. http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/Contaminants/ucm190907.htm
\textsuperscript{14} Luther, M. 2012. Report of FY 2010 nationwide survey of distillers products for antibiotic residues, Center for Veterinary Medicine, FDA, Silver Springs, MD.
\textsuperscript{19} Lactrol- Virginiamycin and Dextrose, Product Data Sheet, Phibro Ethanol Performance, https://www.pahc.com/wp-content/uploads/ProductDataSheets/EPG/Antibiotics/phibro-lactrol-4-4-16.pdf
\textsuperscript{22} Islam, M., R. Toledo, and M.K. Hamdy. 1999. Stability of virginiamycin and penicillin during
Penicillin is significantly inactivated at temperatures of the ethanol distillation process of 100°C.\textsuperscript{23} Temperature conditions in the drying step in Phase I CO1 process and deodorization step in the Phase II RBD process can be as high as 260°C enough to deactivate any Penicillin residues if they are present in the crude corn oil. Penicillin G has high solubility in both water (\(>0.056\text{mol/l or 18704mg/l}\)) and ethanol (\(>0.028\text{mol/l or 9352mg/l}\)).\textsuperscript{24,25,26,27} So, in the unlikely event any Penicillin residues are present in crude corn oil the residues will be removed during contact with aqueous ethanol solutions in the neutralization step of Phase I CO1 process and the water wash step during the refining step of the Phase II RBD process.

**Erythromycin:** The stability of erythromycin is pH and temperature dependent, where it is more stable at the pH range from 7.0 to 8.0 and lower temperatures.\textsuperscript{28} Erythromycin is likely inactivated by the low pH and high temperatures encountered during fermentation and distillation of ethanol. Temperature conditions in the drying step in Phase I CO1 process and deodorization step in the Phase II RBD process can be as high as 260°C which is enough to deactivate any Erythromycin residues if present in the crude corn oil. Further, Erythromycin is soluble in water (2000mg/l) and polar solvents such as ethanol.\textsuperscript{29, 30, 31} So, in the unlikely event any Erythromycin residues are present in the crude corn oil, the residues will be removed during contact with aqueous ethanol solutions in the neutralization step of Phase I CO1 process and the water wash step during the refining step of the Phase II RBD process.

**Tylosin:** Tylosin is not a commonly used antibiotic in the corn fermentation process. Tylosin is most stable at about pH of 3.5 to about pH of 9. Outside of those pH ranges, there is significant inactivation of the antibiotic. In addition, exposure to increased temperatures can lead to inactivation.\textsuperscript{32} Temperature conditions in the drying step in Phase I CO1 process and deodorization step in the Phase II RBD process can be as high as 260°C which is enough to deactivate any Tylosin residues if present in the crude corn oil. Tylosin is approved to be fed to livestock. Further, Tylosin is highly soluble in water at levels of 5000 mg/l and freely soluble in methanol and other lower alcohols.\textsuperscript{33} So, in the unlikely event any Tylosin residues are present in the crude corn oil, the residues will be removed during the contact with aqueous ethanol solutions in the alcohol fermentation. Biomass and Bioenergy 17 :369-376.


\textsuperscript{24} Weiss P.J.; Andrew, M.L.; Wright, W.W. Antibiotics and Chemotherapy 1957, 7, 374.

\textsuperscript{25} David J. Maggs, Chapter 3 - Ocular Pharmacology and Therapeutics, Slatter's Fundamentals of Veterinary Ophthalmology (Fourth Edition), 2008


\textsuperscript{27} E. Tomlinson, A. Regosz, Solubility data series, Antibiotics: 1, beta-lactam antibiotics, Pergamon Press, Vol 16/17 1985


\textsuperscript{29} https://www.chemicalbook.com/ChemicalProductProperty_US_CB8300078.aspx


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neutralization step of Phase I CO1 process and the water wash step during the refining step of the Phase II RBD process.

**Tetracycline:** Tetracycline is not a commonly used antibiotic in the corn fermentation process. Tetracycline is inactivated in acidic conditions (pH < 2) forming anhydroteracycline. 34 Further, Tetracycline has limited solubility in water at levels of 231 mg/l 35 and highly soluble in ethanol at levels of 20,000 mg/ml. 36 So, in the unlikely event any Tetracycline residues are present in the crude corn oil, the residues will be removed during the contact with aqueous ethanol solutions in the neutralization step of Phase I CO1 process and the water wash step during the refining step of the Phase II RBD process.

Q6. On pages 66-68, the notice notes 3 of 5 antibiotics are unstable under acidic conditions (C01 process and degumming) and 4 of 5 antibiotics are unstable to caustic refining. Please provide a narrative on the effect of these processes on the removal of antibiotics and/or their degradants including references or data (e.g., spiked samples) in support. Consider the following in your discussion:

a. Discuss the basis for concluding removal of residues of virginiamycin by deodorization (p. 68). Are other antibiotics or their degradants affected by deodorization?

**Response:**
Antibiotics are inactivated at high temperature conditions. Specifically, virginiamycin is inactivated at temperatures greater than 100°C and penicillin at temperatures greater than 35°C. Temperatures in deodorization process can reach as high as 260°C and will therefore inactivate the antibiotics. However, due the solubility of these virginiamycin and other antibiotics in water and ethanol, they will be removed from the oil in the neutralization step of Phase I CO1 process and the water wash step during the refining step of the Phase II RBD process. Appendix E is updated accordingly.

b. Address solubility of erythromycin in oil based on the data from one of the crude oil samples (page 69). Other than the single batch analysis, there is no supporting information in the notice.

**Response:**
Erythromycin is soluble in water (2000mg/l) and polar solvents such as ethanol. 37, 38, 39 So, in the unlikely event any Erythromycin residues are present in the crude corn oil, the residues will be removed during contact with aqueous ethanol solutions in the neutralization

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c. Address the step(s) of the CO1 or RBD process that removes erythromycin.
   **Response:**
   As addressed in Q5, temperature conditions in the drying step in Phase I CO1 process and deodorization step in the Phase II RBD process can be as high as 260°C which is enough to deactivate any Erythromycin residues if present in the crude corn oil. Further, Erythromycin is soluble in water (2000mg/l) and polar solvents such as ethanol. 40, 41, 42 So, in the unlikely event any Erythromycin residues are present in the crude corn oil, the residues will be removed during contact with aqueous ethanol solutions in the neutralization step of Phase I CO1 process and the water wash step during the refining step of the Phase II RBD process.

d. Address the affinity of antibiotics and their degradants in the oil to the bleaching material proposed for use (bentonite).
   **Response:**
   There is evidence that some of the antibiotics will be adsorbed by soil.43,44 The adsorption of the antibiotics depends on the adsorption potential of the clay. 45 However, due to the solubility of these antibiotics in water and ethanol, the antibiotics will be removed from the oil in the neutralization step of Phase I CO1 process and the water wash step during the refining step of the Phase II RBD process prior to the bleaching step. Appendix E is updated accordingly.

Q7. On page 34, the presumed body weight of 60 kg used in the acceptance criteria rationale for antibiotics would not be appropriate for children. Please discuss how children were considered in the safety evaluation of antibiotic intake.

   **Response:**
   The acceptance criteria for antibiotics are non-detects based on the limit of detection (LOD) of 0.05 ppm. (FDA LIB 4438). The following assessment was conducted to provide support that a non-detection at the LOD 0.05 ppm is safe:
   - Based on 21 CFR §556.750, the ADI for *virginiamycin* is 250 µg/kg bw/day.
   - JECFA (2006) established an ADI of 0–0.7 µg/kg bw for *erythromycin*
   - JECFA (1998) established an ADI of 30 µg/p/d for *penicillin G*.
   - Based on 21CFR §556.750, the ADI for *tetracycline* is 25 µg/kg bw/day
   - JECFA (2008) established an ADI of 0–30 µg/kg bw for *tylosin*.

   Assuming that the daily intake of corn oil of 6g/day (see EDI in Appendix H of the GRN) is exposed at the LOD of 0.05 ppm, for a 10 kg bw of a child, the EDI would be 0.03 µg/kg bw/day.

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43 Meylan WM et al; Environ Sci Technol 26: 1560-67 (1992)
This is well below the ADIs for these antibiotics. Therefore, there is an ample margin of safety when there is no detection at the LOD of 0.05 ppm in the crude corn oil when considering the children population.
Mycotoxin Levels

Q1. Provide a narrative to address the levels of mycotoxins in COZ corn oil compared to corn oil produced by traditional methods.

Response:
Corn is primarily used in four different applications (1) animal feed production, (2) dry milling to produce ethanol, distillers grains and distillers corn oil. (3) wet milling to produce corn starch, corn flour and corn oil (4) distillers to produce industrial grade ethanol. The corn used in all these applications is sourced from the same corn crop across the US. All grain crops are susceptible to fungal infections when specific weather patterns occur during the growing season. These fungi are capable of producing mycotoxins. The most common mycotoxins that are present in corn are aflatoxins, fumonisins and deoxynivalenol. T2-Toxin and Zearalenone are less commonly found in corn crops. FDA acknowledges that the wet-milling is an effective process for removing mycotoxins like aflatoxin and fumonisin from corn starch, corn derived sweeteners and corn oil.46 This is due the high solubility of Aflatxin, fumonisin and deoxynivalenol in water and other aqueous solvents such as ethanol. Various studies, as shown in the sections below, have indicated that the mycotoxins are not major concern in the food products derived from corn through wet milling process. 46

The first step in a wet-milling corn plant is called steeping where all the corn in soaked in 50°C water for about 30-40 hours. This allows the corn to swell and loosen the gluten bonds. In the next step the germ is mechanically separated. Germ is then processed to extract crude corn oil which is then further refined by standard refining process similar to the Phase II RBD process used to produce COz product. The rest of the corn is further processed to separate starch, fiber and other food grade products. 47

Aflatoxin: Predicted water solubility of aflatoxins is in the range of 233 to 994mg/l. 51 Due to its high solubility in water, Aflatoxins are primarily recovered in the steep water. For example, it was reported that up to 50% of the aflatoxin present initially was found in the steep water solubles. Corn germ, from which corn oil is extracted contains up to 10% of the aflatoxins present initially. 48,49, 50

Fumonisin: Water solubility of fumonisins is experimentally tested and is reported at >20,000mg/l. 51 A joint USDA-University of Illinois wet-milling study found that about 40% of fumonisin B1 and B2 were recovered in the gluten and fiber fractions and that of corn germ,

46 Food Safety Information Papers, Corn Refiners Association, Inc. Mycotoxins prepared by WHITE Technical Research group, Revised by DTB Associates, LLP 217/795-4437
48 Romer, T., Detecting mycotoxins in corn and corn milling products, Feedstuffs, 56 (37): 22-23, 1984
51 NTP, US National Toxicology Program (2000) NTP technical report on the toxicology and carcinogenesis studies of fumonisin B1 (CAS No 116355–83-0) in F344/N Rats and B6C3F1 Mice (Feed Studies) (TR 496; NIH Publication No 99–3955). Research Triangle Park, NC

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from where corn oil is extracted, contained about 20% of the initial Fumonisin level.\textsuperscript{52,53}

**Deoxynivalenol:** Predicted water solubility of aflatoxin is 36,000mg/l.\textsuperscript{54} Due to relatively high water solubility, like fumonisin and aflatoxin, the highest concentration of deoxynivalenol was found in steep water.\textsuperscript{55} The lowest levels of deoxynivalenol was found in the germ fraction, where the corn oil is extracted.

Similar to the procedures used in wet milling process, a typical corn ethanol process also starts by grinding the corn followed by soaking the corn in water along with some enzymes at 75-95\textdegree C to allow for the starch, germ and fiber fractions to swell and be released into the water slurry. This slurry is then fermented using yeast. If there are mycotoxins present in the corn, they will preferentially be released into steep water. If the mycotoxins are carried along with the crude corn oil, they will transfer into the aqueous phase during the neutralization step in the Phase I CO1 process, when the crude corn oil is in mixed with aqueous alcohol solutions at 70\textdegree C for 8-10 hours. Further, in the Phase II RBD process, both in the degumming process and refining process, the corn oil is mixed with water at 70-90\textdegree C for 10-40 min during which mycotoxins will transfer into the aqueous phase.

Q2. Provide a narrative to address the removal of mycotoxin residues, if any, by the CO1 process or subsequent chemical refining and/or bleaching steps\textsuperscript{56} Consider the following in a discussion:

a. In Appendix E (p. 66), the notice states near complete adsorption of aflatoxin on bentonite. Indicate if this was determined experimentally or based on a published reference.

**Response:** Greater than 99\% of aflatoxin was adsorbed on to bentonite clay withing 15 min.\textsuperscript{57} Montmorillonite clay, due to its adsorption potential, is also used in animal feed to adsorb aflatoxin residues.\textsuperscript{58}

b. On p. 68, the notice states that 20\% of DON is removed and 30\% of fumonisin is removed by bleaching. We note that the information in the table on p. 68 regarding low affinity of DON (20\% absorbed) and fumonisin (30\% absorbed) for bentonite contradicts

\textsuperscript{52} Saunders, D. F., Meredith, F. I and Voss, K. A, Control of Fumonisin: Effects of processing, Environmental Health Perspectives, 109: 333-6, 2001


\textsuperscript{54} Impact of food processing and detoxification treatments on mycotoxin contamination, Karlovsky, Suman, Berthiller, Meester, Eisenbrand, Perrin, Oswald, Speijers, Chiodini, Recker, Dussort; Mycotoxin Res (2016) 32:179–205

\textsuperscript{55} Lauren, D. R and M. A. Ringrose, Determination of the fate of three Fusarium mycotoxins through wet-milling of maize using an improved HPLC analytical technique, Food Additives and Contaminants, 14 (5): 435-443, 1997

\textsuperscript{56} Park J et al. 2018. Toxins.10:319; Escobar J et al. 2013. Food and Chemical Toxicology. 62: 514-20


\textsuperscript{58} Q. Desheng, L. Fan, Y. Yanhu, and Z. Niya; Poultry Science, Volume 84, Issue 6, 1 June 2005, Pages 959-961
the statement on

**Response:** Appendix E has been updated and is enclosed

c. p. 19 that any residual mycotoxins will be absorbed by bleaching clay. Please clarify and state your conclusions (from laboratory data or published information) regarding how these mycotoxins are removed.

**Response:** There is evidence that some of the mycotoxins will be adsorbed by clay/soil. The adsorption of the mycotoxin depends on the adsorption potential of the clay. However, due to the solubility of these mycotoxins in water and ethanol, the mycotoxins will be removed from the oil in the neutralization step of Phase I CO1 process and the water wash step during the refining step of the Phase II RBD process prior to the bleaching step. Appendix E is updated accordingly.

Q3. On page 34, the notice cites the FDA action level for total aflatoxin and guidance levels for fumonisin and deoxynivalenol. For clarity, do the suppliers of the crude corn oil use corn starting material for the fermentation that meet those acceptance criteria (for use in food and feed)?

**Response:** Suppliers of crude corn oil will use the acceptance criteria on crude corn oil and not on corn starting material.

Q4. Zearalenone has been reported to be present in corn oil (e.g., Escobar et al., 2013) although there are no FDA guidance levels. Is the level of zearalenone considered in the acceptance criteria for the crude corn oil?

**Response:** Zearalenone was not considered in the GRN as there are no established FDA guidance levels for zearalenone in corn. The paper FDA cited by Escobar et al does point to the fact that zearalenone can occur in corn oil. The study found zearalenone in 32% of samples at a mean level of 15µg/kg, a level more than an order of magnitude below the European Commission maximum limit of 400 ppb. Therefore, zearalenone levels in refined corn oil are not expected to raise safety concerns.
Other Contaminants

Q1. Do the contaminant analyses include 2- and 3-monochloropropane diols and glycidyl esters? Please clarify if the refining method incorporates strategies to mitigate formation of these contaminants. 59

Response:

Corn Oil One tested Coz oil samples from three non-consecutive batches for MCPD esters and glycidyl esters. The results are as followed:

<table>
<thead>
<tr>
<th></th>
<th>Batch 1</th>
<th>Batch 3</th>
<th>Batch 5</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCPD Esters, mg/kg of COz</td>
<td>0.42</td>
<td>0.32</td>
<td>0.42</td>
<td>A2LA ISO/IEC 17025:2005 2993-01</td>
</tr>
<tr>
<td>Glycidyl Esters, mg/kg of COz</td>
<td>11.18</td>
<td>0.72</td>
<td>11.67</td>
<td>A2LA ISO/IEC 17025:2005 2993-01</td>
</tr>
</tbody>
</table>

Assuming the average concentration from three tested samples, the daily intake of corn oil of 6g/day (see EDI in Appendix H of the GRN) and a default body weight of 60kg, the following EDI can be estimated and compared to the JECFA limits for these compounds:

<table>
<thead>
<tr>
<th></th>
<th>EDI (µg/kg bw/day)</th>
<th>Exposure Limits –JECFA 83rd report 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCPD Esters</td>
<td>0.039</td>
<td>4 µg/kg bw/day (PMTDI) → (TDI = 0.13 µg/kg bw/day)</td>
</tr>
<tr>
<td>Glycidyl Esters</td>
<td>0.79</td>
<td>2.4 mg/kg bw/day (BMDL_{10})</td>
</tr>
</tbody>
</table>

The EDI for MCPD esters is below the JECFA TDI. The EDI for glycidyl esters has a margin of exposure (MOE) of 3000 based on the JECFA-BMDL. Therefore, these levels in Coz corn oil are not of safety concern.

Q2. The regulation the notice cites (p.15) to indicate the acceptance limit (40 CFR 180 Tolerances and exemptions for pesticide and chemical residues in food) does not include all the pesticides listed in the batch analyses. Please check.

Response: The list of pesticides tested in the COA is obtained from USDA/FSIS Blue Book. 61 United States National Residue Program (NRP) summarizes the process used by the USDA/FSIS, for sampling and testing of FSIS products for chemical compounds of public health concern and are modified annually in response to emerging chemical residue concerns and

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60 https://apps.who.int/iris/bitstream/handle/10665/254893/9789241210027-eng.pdf?sequence=1
improved testing methodologies. The 2018 NRP Residue Sampling Plan focuses on chemical residues in domestic meat, poultry, and egg products and the import reinspection of meat, poultry, and egg products.

Q3. Several of the pesticides listed in the Pesticide/PCB screen have action levels listed in CPG 575.100, i.e. chlordane, lindane, aldrin and dieldrin, BHC, DDT/DDE/TDE. Please confirm that the source material does not exceed action levels for pesticides and that is produced in accordance with good agricultural practices.

**Response:** Levels of the pesticides listed in CPG 575.100 in the source material will not exceed the action levels for the respective pesticides. Also, the levels of the pesticides are non-detects as per the COA’s and therefore below any action levels for these contaminants.
SAFETY DATA SHEET

VOxOUT 70

1 PRODUCT AND COMPANY IDENTIFICATION

Product Identifier: VOxOUT 70
Common Name: MIXTURE
SDS Number: 3000
Revision Date: 2/15/2017
Version: 1
Internal ID: 200C
Product Use: VOC Scavenger
Supplier Details: U.S. Water Services
12270 43rd St. NE
St. Michael, MN 55376

Contact: Non-emergency #: 866-663-7632
Email: SDS@uswaterservices.com
Web: www.uswaterservices.com

EMERGENCY RESPONSE: (ChemTel)
US & Canada: 800-255-3924
International: +01-813-248-0585

HAZARDS IDENTIFICATION

Classification of the substance or mixture

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS):
- Physical, Corrosive to Metals, 1
- Health, Skin corrosion/irritation, 1

GHS Label elements, including precautionary statements

GHS Signal Word: DANGER

GHS Hazard Pictograms:

GHS Hazard Statements:
- H290 - May be corrosive to metals
- H314 - Causes severe skin burns and eye damage

GHS Precautionary Statements:
- P281 - Use personal protective equipment as required.
- P302+352 - IF ON SKIN: Wash with soap and water.
- P305+351+338 - IF IN EYES: Rinse continuously with water for several minutes. Remove contact lenses if present and easy to do. Continue rinsing.
- P301+330+331 - IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
- P315 - Get immediate medical advice/attention.
- P260 - Do not breathe vapours.
Hazards not otherwise classified (HNOC) or not covered by GHS

COMPOSITION/INFORMATION ON INGREDIENTS

Ingredients:

<table>
<thead>
<tr>
<th>Cas#</th>
<th>%</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>10192-30-0</td>
<td>60-70%</td>
<td>Ammonium bisulfite</td>
</tr>
</tbody>
</table>

FIRST AID MEASURES

Inhalation: Remove to fresh air. If breathing is difficult, administer oxygen. If not breathing, give artificial respiration, preferably mouth-to-mouth. GET MEDICAL ATTENTION IMMEDIATELY.

Skin Contact: Immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Get medical attention immediately. Do not reuse clothing and shoes until cleaned.

Eye Contact: Immediately flush eyes with plenty of water for at least 15 minutes while holding eyelids open. Tilt head to avoid contaminating unaffected eye. Get immediate medical attention.

Ingestion: If fully conscious, drink a quart of water. DO NOT induce vomiting. CALL A PHYSICIAN IMMEDIATELY. If unconscious or in convulsions, take immediately to a hospital or a physician. NEVER induce vomiting or give anything by mouth to an unconscious victim. If vomiting occurs spontaneously, keep head below hips to prevent aspiration of liquid into the lungs.

Most important symptoms & effects (acute & delayed):
Eye Contact: CORROSIVE-Causes severe irritation and burns. May cause: permanent eye damage.
Skin Contact: CORROSIVE-Causes severe irritation and burns. Contact may cause: redness, blistering, pain, tissue destruction.
Inhalation: Vapors or mists may irritate: nose. throat. respiratory tract. May cause: coughing, difficulty breathing, tightness of the chest. Extreme exposures may cause: severe irritation, pulmonary edema.
Ingestion: May be corrosive to the gastrointestinal tract. Severe irritation and burns may result. May irritate or burn: mouth, throat, digestive tract. May cause: vomiting. Small amounts of liquid aspirated into the lungs during ingestion or from vomiting may cause pulmonary edema

Indication of need for immediate medical attention: Treat symptomatically. Not potential for anaphylactic shock with allergic individuals.

Special treatment needs: No data available

FIRE FIGHTING MEASURES

Flammability: Nonflammable
Flash Point: None
Flash Point Method: Pensky Martens Closed cup
Burning Rate: No data available
Autoignition Temp: No data available
LEL: Not applicable
UEL: Not applicable

Extinguishing Media:
Suitable: Use extinguishing media suitable for surrounding fire.

Unsuitable: No information available

Hazardous combustion products: Hazardous decomposition products formed under fire conditions- Toxic vapors, sulfur oxides, ammonia.

Unusual Fire or Explosion Hazards: Sulfur dioxide gas will released at a rate increasing with temperature

Special protective equipment/precautions: Wear self-contained breathing apparatus

ACCIDENTAL RELEASE MEASURES

Personal Precautions, Protective equipment, emergency procedures: Corrosive material. Avoid contact with the material. See section 8 of SDS for PPE recommendations

Environmental Precautions: Keep runoff from entering drains or waterways

Spill/Leak procedures: Shut off source of leak if safe to do so. Contain spill, place into drums for proper disposal. Soak up residue with inert absorbent material. Place in non-leaking containers for immediate disposal. Flush remaining area with water to remove trace residue and dispose of properly. Prevent entry into basements, low areas, or confined areas. Avoid direct discharge to sewers and surface waters. Notify authorities if entry occurs.

Cleanup: After collection/absorption of spill, flush away remaining traces with large amounts of water.

REGULATORY REQUIREMENTS: Dispose of recovered material in accordance with all applicable state and federal regulations.

HANDLING AND STORAGE

Handling Precautions: Avoid contact with eyes, skin, and clothing. Use with adequate ventilation. Do not swallow. Avoid breathing vapors, mists, or dust. Do not eat, drink, or smoke in work area. Wash thoroughly after handling. Empty containers retain product residue (vapor, dust, or liquid) and can be dangerous. DO NOT pressurize, cut, weld, braze, solder, drill, grind, or expose such containers to heat, flame, sparks, static electricity, or other source of ignition. They may explode and cause injury or death.

Storage Requirements: CORROSIVE MATERIAL. Store in a cool, well ventilated area, out of direct sunlight. Store in a dry location away from heat. Keep away from incompatible materials. Keep containers tightly closed. Do not store in unlabeled or mislabeled containers. Prolonged exposure to the atmosphere will slowly oxidize this product, releasing sulfur dioxide gas. Do not freeze. Relieve pressure in drums weekly.

EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering Controls: Provide local exhaust ventilation as needed to control misting or vapor accumulation.

Personal Protective Equipment:

HMIS PP, C | Safety Glasses, Gloves, Apron

Respiratory protection: May be required if ventilation is inadequate. If needed use MSHA/NIOSH approved respirator for dusts, mists, and/or SO2 vapors. Seek professional advice prior to respirator selection and use. Follow all requirements of OSHA respirator regulations (29 CFR 1910.134)

Safety Stations: Make emergency eyewash stations, safety/quick-drench showers, and washing facilities available in work area.
General Hygiene: Never eat, drink, or smoke in work areas. Practice good personal hygiene after using this material, especially before eating, drinking, using the toilet, or applying cosmetics. PPE recommendation is advisory only and based on typical use conditions. An industrial hygienist or safety officer familiar with the specific situation of anticipated use must determine actual PPE required when using this product (29 CFR 1910.132)

Exposure Limits:
Sulfur Dioxide gas may be released. Exposure limit for Sulfur Dioxide are 5ppm TWA (OSHA); 5ppm TWA, 5ppm- STEL (ACGIH)

### PHYSICAL AND CHEMICAL PROPERTIES

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Clear, colorless to light yellow</td>
</tr>
<tr>
<td>Physical State</td>
<td>Liquid</td>
</tr>
<tr>
<td>Odor Threshold</td>
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<tr>
<td>Spec Grav./Density</td>
<td>11.59Lb/Gal @25°C</td>
</tr>
<tr>
<td>Viscosity</td>
<td>No data available</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>Not determined</td>
</tr>
<tr>
<td>Flammability</td>
<td>Non Flammable</td>
</tr>
<tr>
<td>Partition Coefficient</td>
<td>No data available</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>Not determined</td>
</tr>
<tr>
<td>pH</td>
<td>5.4 (as is)</td>
</tr>
<tr>
<td>Evap. Rate</td>
<td>Not determined</td>
</tr>
<tr>
<td>Decomp Temp</td>
<td>Not determined</td>
</tr>
<tr>
<td>Odor</td>
<td>Sulfur dioxide smell</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in water</td>
</tr>
<tr>
<td>Percent Volatile</td>
<td>Not determined</td>
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<tr>
<td>Freezing/Melting Pt.</td>
<td>14°F</td>
</tr>
<tr>
<td>Flash Point</td>
<td>Does not Flash</td>
</tr>
<tr>
<td>Vapor Density</td>
<td>Not determined</td>
</tr>
<tr>
<td>VOC</td>
<td>0% (w/w)</td>
</tr>
<tr>
<td>Auto-Ignition Temp</td>
<td>Not Determined</td>
</tr>
<tr>
<td>UFL/LFL</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

### STABILITY AND REACTIVITY

Chemical Stability: Product is stable under normal storage and use conditions.

Conditions to Avoid: Avoid heat, sparks or open flames. Avoid elevated temperatures


Hazardous Decomposition: Toxic vapors, Sulfur dioxide gas, Ammonia.

Hazardous Polymerization: Hazardous polymerization will not occur under normal conditions. Both acidification and heating accelerate the release of Sulfur dioxide fumes. Alkaline materials will accelerate the evolution of ammonia.

### TOXICOLOGICAL INFORMATION

Acute Toxicity: No data available

Skin Corrosion/Irritation: Corrosive. Causes severe irritation and burns. Contact may cause redness, blistering, pain, tissue destruction

Serious eye damage/Irritation: Corrosive. Causes severe irritation and burns. May cause permanent eye damage.
Respiratory or skin sensitization: Vapors or mists may irritate nose, throat, respiratory tract. May cause coughing, difficulty breathing, tightness of the chest. Extreme exposures may cause severe irritation, pulmonary edema.
Specific target organ toxicity (single exposure): No data available
Specific target organ toxicity (repeated exposure): No data available
Aspiration hazard: No data available
Carcinogenicity: No carcinogenic effects are known for the components of this product
Germ Cell Mutagenicity: No mutagenic effects are known for the components of this product
Teratogenicity: No teratogenic effects are known for the components of this product

ECOLOGICAL INFORMATION

Aquatic Toxicity No data available
Elimination (persistence & degradability): No data available
Bioaccumulative potential: No data available
Mobility in soil: No data available
Other adverse effects: No data available

DISPOSAL CONSIDERATIONS

Dispose of in accordance with local regulations.

This material should be fully characterized for toxicity and possible reactivity prior to disposal (40 CFR 261). Use which results in chemical or physical change or contamination may subject it to regulation as a hazardous waste. Along with properly characterizing all waste materials, consult state and local regulations regarding the proper disposal of this material.

Container contents should be completely used and containers should be emptied prior to discard. Container rinseate could be considered a RCRA hazardous waste and must be disposed of with care and in full compliance with federal, state and local regulations. Larger empty containers, such as drums, should be returned to the distributor or to a drum reconditioner. To assure proper disposal of smaller empty containers, consult with state and local regulations and disposal authorities.

TRANSPORT INFORMATION

UN2693, Bisulfites, aqueous solutions, n.o.s., 8, PGIII, (Ammonium Bisulfite)
Certain shipping modes or package sizes may have exceptions from the transport regulations. The classification provided may not reflect those exceptions and may not apply to all shipping modes or package sizes.

DOT Transportation data (49 CFR 172.101)
See section 15 for information on Reportable Quantity chemicals (RQ)

REGULATORY INFORMATION

Component (CAS#) [%] - CODES

RQ(5000LBS), Ammonium bisulfite (10192-30-0) [60-70%] CERCLA, CSWHS, MASS, PA, TSCA

Regulatory CODE Descriptions

------------------------------------------------------------------

RQ = Reportable Quantity  
CERCLA = Superfund clean up substance  
CSWHS = Clean Water Act Hazardous substances  
MASS = MA Massachusetts Hazardous Substances List  
PA = PA Right-To-Know List of Hazardous Substances  
TSCA = Toxic Substances Control Act  

SARA TITLE III: Toxic Chemical List (SARA 313): This product does not contain any chemicals subject to routine annual toxic chemical release reporting.  
Extremely Hazardous Substance (SARA 302/304): This product does not contain any extremely hazardous substances subject to emergency planning requirements.  
SARA 312: Acute  
California Proposition 65: May contain the following in trace amounts: Sulfer Dioxide  
RCRA: Material as supplied is considered: Corrosive, D002

16 OTHER INFORMATION

HMIS III: Health = 3, Fire = 0, Physical Hazard = 0  
HMIS PPE: C - Safety Glasses, Gloves, Apron

Author: U.S. Water Services

Revision Notes: Updated to GHS format

Disclaimer:  
Although reasonable care has been taken in the preparation of this document, we extend no warranties and make no representations as to the accuracy or completeness of the information contained herein, and assume no responsibility regarding the suitability of this information for the user's intended purposes or for the consequences of its use. Each individual should make a determination as to the suitability of the information for their particular purpose(s). The above information is not claiming characteristics of the product in term of legal claims of performance / guarantee. This information only describes safety measures and no liability may arise from the use or application of the product described herein. This information is given in good faith and based on our current knowledge of the product.
SECTION 1. PRODUCT AND COMPANY IDENTIFICATION

Product name: DuPont™ FermaSure® XL
MSDS Number: 130000043784
Product Use: Formulation, Processing aid, Fermentation
Manufacturer: DuPont
1007 Market Street
Wilmington, DE 19898
Product Information: 1-800-441-7515 (outside the U.S. 1-302-774-1000)
Medical Emergency: 1-800-441-3637 (outside the U.S. 1-302-774-1139)
Transport Emergency: CHEMTREC: 1-800-424-9300 (outside the U.S. 1-703-527-3887)
Importer/Distributor: International Dioxcide, Inc., A DuPont Subsidiary, 40 Whitecap Drive, North Kingstown, RI 02852

SECTION 2. HAZARDS IDENTIFICATION

Potential Health Effects
Skin
Oxychlorine compounds: May cause: Corrosion with pain, ulceration or blisters, cracking or peeling of skin.

Eyes
Oxychlorine compounds: Corrosive, may cause permanent eye injury if not promptly treated. May cause: Tearing, pain, redness, swelling, ulceration, visual impairment, or blindness.

Inhalation
Oxychlorine compounds: Causes respiratory tract irritation. May cause: Cough, sneezing, runny nose, sore throat, or shortness of breath.

Repeated exposure: Adverse effects from repeated ingestion may include: Gastrointestinal effects. Abnormal decrease in number of red blood cells (anaemia) which could produce tiredness, rapid heartbeat, dizziness, pale skin, leg cramps, shortness of breath. Altered blood chemistry.

Target Organs: Blood

Carcinogenicity: None of the components present in this material at concentrations equal to or greater than 0.1% are listed by IARC, NTP, or OSHA, as a carcinogen.

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

<table>
<thead>
<tr>
<th>Component</th>
<th>CAS-No.</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxychlorine compounds</td>
<td></td>
<td>15 - 25 %</td>
</tr>
<tr>
<td>Water</td>
<td>7732-18-5</td>
<td>75 - 85 %</td>
</tr>
</tbody>
</table>

SECTION 4. FIRST AID MEASURES

Skin contact: Take off contaminated clothing and shoes immediately. Wash off immediately with plenty of water. Call a poison control center or doctor for treatment advice.

Eye contact: Rinse immediately with plenty of water and seek medical advice.
Material Safety Data Sheet

**DuPont™ FermaSure® XL**

Version 3.0

Revision Date 10/01/2012  Ref. 130000043784

**Inhalation**:
Move to fresh air. If not breathing, give artificial respiration. Call a poison control center or doctor for treatment advice.

**Ingestion**:
Call a poison control center or doctor for treatment advice. Do not induce vomiting without medical advice. Never give anything by mouth to an unconscious person.

**Notes to physician**:
Probable mucosal damage may contraindicate the use of gastric lavage.

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**SECTION 5. FIREFIGHTING MEASURES**

**Flammable Properties**

- **Flash point**
  - does not flash

**Fire and Explosion Hazard**
Drying of this product on clothing or combustible materials may cause fire.

**Suitable extinguishing media**
Water

**Firefighting Instructions**
Wear self-contained breathing apparatus (SCBA). Wear suitable protective equipment.

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**SECTION 6. ACCIDENTAL RELEASE MEASURES**

**NOTE**: Review FIRE FIGHTING MEASURES and HANDLING (PERSONNEL) sections before proceeding with clean-up. Use appropriate PERSONAL PROTECTIVE EQUIPMENT during clean-up.

**Safeguards (Personnel)**
Wear personal protective equipment. Avoid contact with the skin and the eyes.

**Spill Cleanup**
Dilute with water. Pick up and transfer to properly labelled containers. After cleaning, flush away traces with water.

**Accidental Release Measures**
Prevent material from entering sewers, waterways, or low areas. Do not allow to dry.
SECTION 7. HANDLING AND STORAGE

Handling (Personnel)  : Use only in well-ventilated areas. Avoid contact with skin, eyes and clothing. Wash hands before breaks and at the end of workday.

Handling (Physical Aspects)  : Avoid letting the product become dry.

Storage  : Keep tightly closed in a dry, cool and well-ventilated place. Keep away from food, drink and animal feedingstuffs. Avoid heat, freezing and ultraviolet light. Do not allow to dry. Keep away from: Strong acids and oxidizing agents

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering controls  : Ensure adequate ventilation, especially in confined areas.

Personal protective equipment

Respiratory protection  : Where there is potential for airborne exposures in excess of applicable limits, wear approved respiratory protection with dust/mist cartridge. Provide adequate ventilation. In case of insufficient ventilation, wear suitable respiratory equipment.

Hand protection  : Additional protection: Impervious gloves

Hand protection  : Material: Polyvinyl chloride - PVC

Eye protection  : Wear coverall chemical splash goggles. Additionally wear a face shield where the possibility exists for face contact due to splashing, spraying or airborne contact with this material.

Skin and body protection  : Where there is potential for skin contact, have available and wear as appropriate, impervious gloves, apron, pants, jacket, hood and boots.

Protective measures  : Avoid exposure - obtain special instructions before use. Wear suitable gloves and eye/face protection.

Exposure Guidelines
Material Safety Data Sheet

**DuPont™ FermaSure® XL**

Version 3.0

Revision Date 10/01/2012

Ref. 130000043784

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**Exposure Limit Values**

None established.

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**SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES**

- **Form**: liquid
- **Color**: light yellow
- **Odor**: odourless, slight chlorine
- **pH**: 9.5 - 9.7
- **Freezing point**: ca. -18 °C (0 °F)
- **Crystallization temperature**: ca. -12 °C (10 °F)
- **Boiling point**: ca. 106 °C (223 °F)
- **Density**: ca. 9.9 lb/gal at 20 °C (68 °F)
- **Specific gravity**: ca. 1.18 - 1.21
- **Water solubility**: miscible

---

**SECTION 10. STABILITY AND REACTIVITY**

- **Stability**: Stable at normal temperatures and storage conditions. Decomposes on heating.
- **Conditions to avoid**: Stable under normal conditions. Decomposes on heating.
- **Incompatibility**: Strong acids and oxidizing agents Organic materials, chlorinated compounds, Reducing agents
- **Hazardous decomposition products**: Hazardous decomposition products: Chlorine, Chlorine dioxide...%
- **Hazardous reactions**: Contact with acids, organic materials, reducing agents and oxidizing agents will release toxic gases of chlorine and/or chlorine dioxide.
### SECTION 11. TOXICOLOGICAL INFORMATION

<table>
<thead>
<tr>
<th>Material</th>
<th>Dermal LD50</th>
<th>Oral LD50</th>
<th>Skin irritation</th>
<th>Eye irritation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DuPont™ FermaSure® XL</strong></td>
<td>&gt; 2,000 mg/kg, rat</td>
<td>1,075 mg/kg, rat</td>
<td>Non-corrosive</td>
<td>Risk of serious damage to eyes. Information given is based on data obtained from similar product.</td>
</tr>
</tbody>
</table>

**Oxychlorine compounds**

<table>
<thead>
<tr>
<th>Inhalation 4 h LC50</th>
<th>Skin sensitization</th>
<th>Repeated dose toxicity</th>
<th>Carcinogenicity</th>
<th>Mutagenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.23 mg/l, rat</td>
<td>Animal test did not cause sensitization by skin contact., guinea pig</td>
<td>Oral rat 1 y Target Organs: Blood Gastrointestinal effects, Abnormal decrease in number of red blood cells, Abnormal decrease in red-blood-cell haemoglobin (hemoglobinemia) Oral rat 14 d altered hematology, altered urinalysis results Oral Monkey altered hematology, altered blood chemistry</td>
<td>Animal testing did not show any carcinogenic effects.</td>
<td>Tests on bacterial or mammalian cell cultures did not show mutagenic effects.</td>
</tr>
</tbody>
</table>
Animal testing did not show any mutagenic effects.

Reproductive toxicity: Animal testing showed effects on reproduction at levels equal to or above those causing parental toxicity.

Teratogenicity: Animal testing showed effects on embryo-fetal development at levels equal to or above those causing maternal toxicity.

SECTION 12. ECOLOGICAL INFORMATION

Aquatic Toxicity
Oxychlorine compounds
96 h LC50: Cyprinodon variegatus (sheepshead minnow) 105 mg/l

96 h ErC50: Scenedesmus capricornutum (fresh water algae) 1 mg/l

48 h EC50: Daphnia magna (Water flea) < 1.0 mg/l

96 h LC50: Americamysis bahia (mysid shrimp) 0.65 mg/l

Environmental Fate
Oxychlorine compounds
Biodegradability: Readily biodegradable.

Additional ecological information: No data is available on the product itself.

SECTION 13. DISPOSAL CONSIDERATIONS

Waste Disposal: Treatment, storage, transportation, and disposal must be in accordance with applicable federal, state/provincial, and local regulations.

Environmental Hazards: Empty containers should be taken to an approved waste handling site for recycling or disposal. If recycling is not practicable, dispose of in compliance with local regulations.
SECTION 14. TRANSPORT INFORMATION

Not classified as dangerous in the meaning of transport regulations.

SECTION 15. REGULATORY INFORMATION

Other regulations : For professional users only.
TSCA : On the inventory, or in compliance with the inventory
SARA 313 Regulated Chemical(s) : SARA 313: This material does not contain any chemical components with known CAS numbers that exceed the threshold (De Minimis) reporting levels established by SARA Title III, Section 313.
California Prop. 65 : Chemicals known to the State of California to cause cancer, birth defects or any other harm: none known
NJ Right to Know Regulated Chemical(s) : Substances on the New Jersey Workplace Hazardous Substance List present at a concentration of 1% or more (0.1% for substances identified as carcinogens, mutagens or teratogens): Sodium chlorite

SECTION 16. OTHER INFORMATION

HMIS
Health : 2
Flammability : 1
Reactivity/Physical hazard : 0
PPE : Personal Protection rating to be supplied by user depending on use conditions.
Material Safety Data Sheet

DuPont™ FermaSure® XL

Version 3.0

Revision Date 10/01/2012 Ref. 130000043784

The DuPont Oval Logo is a registered trademark of E.I. du Pont de Nemours and Company.

Contact person : MSDS Coordinator, DuPont Chemicals and Fluoroproducts, Wilmington, DE 19898, (800) 441-7515

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

Significant change from previous version is denoted with a double bar.
BOILER MP

1 PRODUCT AND COMPANY IDENTIFICATION

Product Identifier: BOILER MP
Common Name: MIXTURE
SDS Number: 0250
Revision Date: 3/27/2015
Version: 2
Internal ID: 200C
Product Use: BOILER WATER TREATMENT
Supplier Details: U.S. Water Services
12270 43rd St. NE
St. Michael, MN 55376

Contact: Non-emergency #: 866-663-7632
Email: SDS@uswaterservices.com
Web: www.uswaterservices.com

EMERGENCY RESPONSE: (ChemTel)
US & Canada: 800-255-3924
International: +01-813-248-0585

2 HAZARDS IDENTIFICATION

Classification of the substance or mixture

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS):

Health, Acute toxicity, 5 Oral
Health, Acute toxicity, 5 Dermal
Health, Specific target organ toxicity - Single exposure, 3
Health, Serious Eye Damage/Eye Irritation, 2 A
Health, Skin corrosion/irritation, 3

GHS Label elements, including precautionary statements

GHS Signal Word: WARNING

GHS Hazard Pictograms:

GHS Hazard Statements:

H303 - May be harmful if swallowed
H313 - May be harmful in contact with skin
H335 - May cause respiratory irritation
H319 - Causes serious eye irritation
H316 - Causes mild skin irritation

GHS Precautionary Statements:

P102 - Keep out of reach of children.
P281 - Use personal protective equipment as required.
P302+352 - IF ON SKIN: Wash with soap and water.
P305+351+338 - IF IN EYES: Rinse continuously with water for several minutes. Remove contact lenses if present and easy to do. Continue rinsing.
P301+330+331 - IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
P304+340 - IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.

Hazards not otherwise classified (HNOC) or not covered by GHS

PPE recommendation is advisory only and based on typical use conditions. An industrial hygienist or safety officer familiar with the specific situation of anticipated use must determine actual PPE required when using this product (29 CFR 1910.132)

3 COMPOSITION/INFORMATION ON INGREDIENTS

Ingredients:

<table>
<thead>
<tr>
<th>Cas#</th>
<th>%</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1310-73-2</td>
<td>&lt;5</td>
<td>Sodium hydroxide</td>
</tr>
</tbody>
</table>

4 FIRST AID MEASURES

Inhalation: Remove from contamination. If person has stopped breathing administer artificial respiration. Seek medical attention.

Skin Contact: Wash off with soap and plenty of water. Remove contaminated garments and wash or destroy. Seek medical attention if irritation develops. Consult a physician if irritation develops.

Eye Contact: Flush eyes with plenty of running water for 15 minutes. Seek medical attention.

Ingestion: If conscious, give plenty of water. If discomfort or other symptoms develop, seek medical attention. Do not induce vomiting unless directed to do so by medical personnel.

Most important symptoms & effects (acute & delayed): No data available

Indication of need for immediate medical attention: None

Special treatment needs: None

5 FIRE FIGHTING MEASURES

Flammability: Not flammable
Flash Point: None
Flash Point Method: Pensky Martens Closed cup
Burning Rate: No data available
Autoignition Temp: No data available
LEL: Not applicable
UEL: Not applicable

Extinguishing Media:
**SAFETY DATA SHEET**

**BOILER MP**

Suitable: Use extinguishing media suitable for surrounding fire.

Unsuitable: No information available

Hazardous combustion products: Hazardous decomposition products formed under fire conditions- Carbon oxides, and other hazardous compounds

Unusual Fire or Explosion Hazards: None known

Special protective equipment/precautions: Wear self-contained breathing apparatus

## 6 ACCIDENTAL RELEASE MEASURES

Personal Precautions, Protective equipment, emergency procedures: Avoid contact with the material. See section 8 of SDS for PPE recommendations

Environmental Precautions: Keep runoff from entering drains or waterways

Spill/Leak procedures: Contain spill or leak. Dike area if necessary to prevent spill from spreading or entering sewers and waterways. Recover as much as possible then absorb remainder with inert material. Place into closed container for disposal.

Regulatory Requirements: Dispose of recovered material in accordance with all applicable state and federal regulations.

## 7 HANDLING AND STORAGE

Handling Precautions: Avoid contact with eyes, skin, or clothing. Do not taste or swallow. Do not inhale vapor or mist. Use with adequate ventilation. For industrial use only!

Storage Requirements: Keep away from children. Store in closed containers away from temperature extremes and incompatible materials.

Store in properly labeled containers in accordance with all local, state and federal guidelines.

## 8 EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering Controls: Provide local exhaust ventilation as needed to control misting.

Personal Protective Equipment: HMIS PP, C | Safety Glasses, Gloves, Apron

Respiratory protection: If needed use MSHA/NIOSH approved respirator for dusts and mists. Seek professional advice prior to respirator selection and use. Follow all requirements of OSHA respirator regulations (29 CFR 1910.134)

Safety Stations: Make emergency eyewash stations, safety/quick-drench showers, and washing facilities available in work area.

General Hygiene: Never eat, drink, or smoke in work areas. Practice good personal hygiene after using this material, especially before eating, drinking, using the toilet, or applying cosmetics.

PPE recommendation is advisory only and based on typical use conditions. An industrial hygienist or safety officer familiar with the specific situation of anticipated use must determine actual PPE required when using this product (29 CFR 1910.132)

**Exposure Limits:**

OSHA (TWA)/PEL: Sodium Hydroxide 2 mg/m³

NIOSH (REL): Sodium Hydroxide 2 mg/m³
PHYSICAL AND CHEMICAL PROPERTIES

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance:</td>
<td>Clear, yellow</td>
</tr>
<tr>
<td>Physical State:</td>
<td>Liquid</td>
</tr>
<tr>
<td>Odor Threshold:</td>
<td>Not determined</td>
</tr>
<tr>
<td>Spec Grav./Density:</td>
<td>9.26 lb/gal</td>
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<tr>
<td>Viscosity:</td>
<td>Not determined</td>
</tr>
<tr>
<td>Boiling Point:</td>
<td>Similar to water</td>
</tr>
<tr>
<td>Partition Coefficient:</td>
<td>Not determined</td>
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<tr>
<td>Vapor Pressure:</td>
<td>Similar to water</td>
</tr>
<tr>
<td>pH:</td>
<td>12-13</td>
</tr>
<tr>
<td>Evap. Rate:</td>
<td>Not determined</td>
</tr>
<tr>
<td>Decomp Temp:</td>
<td>Not determined</td>
</tr>
<tr>
<td>Odor:</td>
<td>Mild</td>
</tr>
<tr>
<td>Solubility:</td>
<td>Complete in water</td>
</tr>
<tr>
<td>Freezing/Melting Pt.:</td>
<td>30°F</td>
</tr>
<tr>
<td>Flash Point:</td>
<td>None</td>
</tr>
<tr>
<td>Vapor Density:</td>
<td>Not determined</td>
</tr>
<tr>
<td>Auto-Ignition Temp:</td>
<td>Not determined</td>
</tr>
<tr>
<td>UFL/LFL:</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

STABILITY AND REACTIVITY

- Stability: Product is stable under normal storage and use conditions.
- Conditions to Avoid: Avoid temperature extremes. Protect from freezing.
- Materials to Avoid: Strong Oxidizing Agents may cause exothermic reaction, Strong Acids.
- Decomposition: Hazardous. Thermal decomposition may produce carbon oxides and other toxic compounds.
- Polymerization: Will not occur.

TOXICOLOGICAL INFORMATION

- Acute Toxicity: Oral LD₅₀ (rat) > 5,000 mg/kg (estimated)
- Skin Corrosion/Irritation: No data available
- Serious eye damage/irritation: No data available
- Respiratory or skin sensitization: No data available
- Specific target organ toxicity (single exposure): No data available
- Specific target organ toxicity (repeated exposure): No data available
- Aspiration hazard: No data available
- Carcinogenicity: No carcinogenic effects are known for the components of this product
- Germ Cell Mutagenicity: No mutagenic effects are known for the components of this product
- Teratogenicity: No teratogenic effects are known for the components of this product

ECOLOGICAL INFORMATION

- Aquatic Toxicity:
  - Ceriodaphnia dubia: LC₅₀ (48h) > 1,000 mg/L
  - Daphnia magna: LC₅₀ (48h) > 3,000 mg/L
  - Fathead minnow: LC₅₀ (96h) > 8,000 mg/L
- Elimination (persistence & degradability): No data available
- Bioaccumulative potential: No data available
- Mobility in soil: No data available
- Other adverse effects: No data available
13 DISPOSAL CONSIDERATIONS

Dispose of in accordance with local regulations.

This material should be fully characterized for toxicity and possible reactivity prior to disposal (40 CFR 261). Use which results in chemical or physical change or contamination may subject it to regulation as a hazardous waste. Along with properly characterizing all waste materials, consult state and local regulations regarding the proper disposal of this material.

Container contents should be completely used and containers should be emptied prior to discard. Container rinseate could be considered a RCRA hazardous waste and must be disposed of with care and in full compliance with federal, state and local regulations. Larger empty containers, such as drums, should be returned to the distributor or to a drum reconditioner. To assure proper disposal of smaller empty containers, consult with state and local regulations and disposal authorities.

14 TRANSPORT INFORMATION

UN1760, Corrosive liquids, n.o.s., 8, PGIII, (Sodium Hydroxide)

DOT Transportation data (49 CFR 172.101)

See section 15 of SDS for information on Reportable Quantity chemicals (RQ)

15 REGULATORY INFORMATION

Component (CAS#) [%] - CODES

RQ(1000LBS), Sodium hydroxide (1310-73-2) [< 5] CERCLA, CSWHS, MASS, OSHAWAC, PA, TSCA, TXAIR

Regulatory CODE Descriptions

RQ = Reportable Quantity
CERCLA = Superfund clean up substance
CSWHS = Clean Water Act Hazardous substances
MASS = MA Massachusetts Hazardous Substances List
OSHAWAC = OSHA Workplace Air Contaminants
PA = PA Right-To-Know List of Hazardous Substances
TSCA = Toxic Substances Control Act
TXAIR = TX Air Contaminants with Health Effects Screening Level

TSCA: All components of this product are listed (or are not required to be listed) in the TSCA inventory
EPA / CERCLA / SARA TITLE III:
Toxic Chemical List (SARA 313): This product does not contain any chemicals subject to routine annual toxic chemical release reporting.
Extremely Hazardous Substance (SARA 302/304): This product does not contain any extremely hazardous substances subject to emergency planning requirements.
SARA 312: Acute
RCRA: Corrosive, D002
OTHER INFORMATION

HMIS III: Health = 2, Fire = 0, Physical Hazard = 0
HMIS PPE: C - Safety Glasses, Gloves, Apron

Author: U.S. Water Services

Revision Notes: Updated to GHS format

Disclaimer:
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