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## Consulting in Human Health, Toxicology & Regulatory Affairs

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## Reporting by business operators of the food sector with respect to the characterization of Plant preparations

### BabyCalm by HISUNIT

Jerusalem, Israel

August 16, 2017

Report prepared by:

#### **Dr. Yehoshua Maor**

Expert in pharmacology, toxicology and regulatory aspects of medicines and food supplements.

Product Name: BabyCalm NATURAL COLIC DROPS

Producer: **Hisunit** Ltd. 6, Ha'harash St. Ashkelon, 8783787 - Israel

#### **1. Plants in the formula**

##### **• Scientific name**

-*Foeniculum vulgare var. dulce* -  
*Pimpinella anisum* L. -*Mentha piperita*  
L.

##### **• Vernacular names**

-Fennel oil sweet;  
-Aniseed oil;  
- Peppermint oil

##### **• Parts used**

-Sweet fennel oil is extracted from crushed seeds by steam distillation. -Aniseed oil is extracted from the dried ripe fruit and seeds by steam distillation. - Peppermint oil is extracted from the whole plant above ground just before flowering. The oil is extracted by steam distillation from the fresh or partly dried plant.

##### **• Geographical origin**

-Unspecified, available from a number of origins from the supplier R.C.Treant & Co. Ltd. – USA.

- **Conditions of culture and harvesting**

Certified organic essential oils and pressed seed oils.

- 2. **Plant raw material used to make the preparation of plant**

- Specifications in accordance with reference standards
  - Fennel oil sweet;
  - Aniseed oil;
  - Peppermint oil

Manufacturing process for the preparation of plant

- Stages of manufacture and batch size
- Description of manufacturing processes (including information on substances entering the process as well as the ratio between the plant and the extract)
- **Special precautions (light, temperature ...)**

No special precautions concern the final product. However, in order to ensure optimal activity of the components of the formula it is recommendable to keep the product in a cool dry place.

- **Processes of disposal of the components at risk**

No special process of disposal is required for herbal medicines in Israel, especially in view of the fact that there is no component at risk in the formula.

- 4. **Preparation of plant and finished product • Criteria for Standardization (constituents responsible for physiological effects.** The standardization of the constituents follows the professional literature, namely, the following pharmacopeias:

1- Newall CA, Anderson LA, Phillipson JD. Herbal Medicines: A Guide for Health Care Professionals. London: Pharmaceutical Press, 1996

2-British Herbal Pharmacopoeia. Keighlev: British Herbal Medicine

Association, 1983 3- Mills SY. The dictionary of modern Herbalism Wellingborough:Thorsons, 1985 4- Martindale, The Extra

Pharmacopoeia: 30th Edition. (Revnolds JEF, editor). London: The Pharmaceutical Press, 1993

5-ESCOP monographs on the medicinal uses of plant drugs. Fascicule 3. Devon, European Scientific Cooperative on Phytotherapy, 1997. Hansel R.Phytopharmaka, 2nd ed. Berlin, Springer-Verlag, 1991.

6-British pharmacopoeia. Vol. I (International edition and addendum). London, Her Majesty's Stationery Office, 1995

7-European pharmacopoeia, 3rd ed. Strasbourg, Council of Europe, 1996.

- **relevant markers for the identification of the plant constituents at risk (toxicological)** Does not apply
- **Specifications (quantitative levels per recommended daily and 100 g, constituents responsible for the physiological effects and markers)**

Constituent of the formula	% in the formula	Min-Max dose recommended By the manufacturer	Min-Max dose according to the pharmacopeias.	Ratio between the recommended dose and the pharmacopeias.
Anise oil ( <i>Pimpinella anisum L.</i> )	0.17%	Min for 8meals/day : <b>0.0068 ml.</b> Max for 8 meals/day: <b>0.0136 ml.</b>	0.05-0.2 ml 3 times a day	<b>4.53%-9.06%</b> of the daily recommended dose as concentrate
Fennel oil ( <i>Foeniculum vulgare var. dulce</i> )	0.17%	Min for 8 meals/day : <b>0.0068 ml.</b> Max for 8 meals/day: <b>0.0136 ml.</b>	1-6 gr of seeds or equivalent, 3 times a day	<b>4.53%-9.06%</b> of the daily recommended dose as concentrate
Peppermint oil ( <i>Mentha piperita L.</i> )	0.085%	Min for 8 meals/day : <b>0.0034 ml.</b> Max for 8 meals/day: <b>0.0068 ml.</b>	0.2-0.4 ml 3 times a day	<b>1.14%-2.28%</b> of the daily recommended dose as concentrate
Glycerin syrup – E422	99.575%			

- **Physical and chemical properties of the constituents of interest (stability)**

High degree of stability for the 3 years period of validity for all the constituents of the formula.

- **Criteria of purity (microbiology, heavy metals, residual solvents, other contaminants)**

See attached certificate of analysis

- **Justification for the formulation**

The formula contains three herbal medicines which have long been safely used in traditional medicine for infantile colic. The dose recommended by the manufacturer stands in accordance to the pharmacopeias cited above.

The product BabyCalm bears similarities to another product known as fennel honey which according to the American Botanical Council has the following recommended **dosage and administration** (10):

Fennel honey or fennel syrup with 0.5 g fennel oil/kg [=0.5:1000 (w/w)]

The BabyCalm formula meets these requirements.

- **Storage conditions:** in a cool dry place
- **Post-marketing surveillance**

No national pharmacopoeia is currently used, and there is no information available about national monographs. The same GMP rules are required for the manufacture of herbal medicines as for conventional pharmaceuticals. Compliance with these requirements is ensured through inspections. Safety requirements are the same as for conventional pharmaceuticals, but also include the special requirement of traditional use without demonstrated harmful effects.

**Herbal medicines are sold worldwide in pharmacies as over the counter remedies.**

## Annex I

### Reporting by business operators

### REGARDING FOOD SAFETY PREPARATIONS PLANT

#### 1. Exposure

- Power consumption forecast for the preparation of plant, including the quantity (exposure maximum and average), frequency and duration.

Does not apply.

- Potential consumption of the preparation plant through other sources (other food, medicine).

Does not apply.

- Terms of use for the preparation of plant.

Does not apply.

- Data known to use the preparation of plant.

Does not apply.

NB.: The product is a mixture of very small percentage of essential oils in Glycerin syrup – E422. The raw materials come from GMP certified factories in the US and Israel.

#### 2. toxicological Data

- Constituents responsible for adverse events (identification, dosage) • toxicology data from the literature (safety limits or dose tolerable in active substances or tracers, limits secondary metabolites potentially toxic)
- Changes in the manufacturing process
- Risk analysis demonstrating the safety under the proposed conditions (target portion recommended daily ...)

Information collected through monitoring of the occurrence of incidents in the world. This information also concern species.

Warnings against potential, particularly for certain populations (pregnant women, breastfeeding women, infants and young children...). Known molecular interactions (including drug).

In a publication by the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 1999 (See reference 1), there is a suggestion to a cancer risk in estragole a component of the fennel essential oil as a monosubstance as opposed to a mixture of substances in the fennel oil in which estragole represents at maximum 5% (5).

In these official statements estragole is classified as a genotoxic carcinogen (4) (Especially as hepatocarcinogen).

The data which support these reports are exclusively based on animal experiments with CD1 deficient mouse lines, with partly very high doses (0,051000 mg / kg body weight (BW) The rats were fed or were administered orally fennel seeds (6-9).

The product BabyCalm is also known as fennel honey which according to the American Botanical Council has the following recommended dosage and administration (10):

Fennel honey or fennel syrup with 0.5 g fennel oil/kg [=0.5:1000 (w/w)] The BabyCalm formula meets these requirements.

Pharmacological calculations: Even using extrapolation methods and considering estragole to be a major component of up to 20% of the fennel oil (as opposed to the usually accepted 5%), it will be found to have 0.34 g of estragole in 1 L. Since the molecular weight of the monosubstance is 148 D, the concentrated formula will be 2 mM solution. Since one bottle of the product comes with 15 mL to be diluted to 50 mL, which will give a final concentration of 600  $\mu$ M (that will already be in the ppm range).

Each dose of 10 drops will have a concentration of 2.95  $\mu$ M. The final concentration/body weight in a baby of 3.5 kg will be approximately 800 nM and in a baby weighing 7 kg will be 400 nM.

It is noteworthy the difference between the animal experiments (chronic) which was in the mM range and the use of the BabyCalm formula in babies (subacute) in the nM range. The concentrations in the animal experiments are at least 2000 times higher than that of the formula BabyCalm.

Therefore, direct translation of animal experiments to the human situation is at least problematic for numerous reasons (11). In addition, no clinical, epidemiological or experimental evidence exists, that would confirm the supposed cancer risk. A critical evaluation of the respective studies leads to the conclusion, that a cancer risk, should it really exist, would be negligible (11).

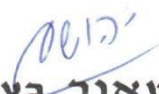
### **Formula safety:**

All components of the formula possess:

- 1- FDA GRAS (generally regarded as safe) list;
- 2- Pharmacopoeial Standards for pediatric doses (5% of an adult dose);
- 3- American Botanical Council approved for infants as fennel honey (syrup);

For the majority of the beneficial aspects, traditionally attributed to fennel components, clinical and experimental evidence are available by now (12). Therefore, we are able to endorse fennel oil in the formula **BabyCalm** as safe and to recommend its use even in pediatric doses.

Sincerely,



פיטאור בע"מ  
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PHYTOR LTD.

Yehoshua Maor

Ph.D., M.Sc., B.Pharm.

### **About my training:**

- Bachelor's degree in Pharmacy ( B.Pharm , Brazil )
- Medicinal Chemistry degree ( M.Sc. , Hebrew University)
- PhD in Medicinal Chemistry and Molecular Biology ( PhD, Hebrew University) •Post - Doctoral School of Medicine and Harvard University , Boston , USA, on Pharmacology of cardiovascular system.
- Former** coordinator of the Hebrew University Center of Excellence in Agriculture and Environmental Health.
- Currently** full member of the SOT – Society of Toxicology – USA.
- Lecturer of Toxicology at the Faculty of Medicine, school of Pharmacy, Hebrew University - Ein Kerem campus - Jerusalem.
- Senior consultant at Phytor Ltd. Engaged in consulting in pharmacology, toxicology and regulatory aspects of new drugs and chemical substances of medicinal plants and food additives.



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Evidence on the carcinogenicity of estragole. Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 1999.  
[www.oehha.ca.gov/prop65/pdf/estragf.pdf](http://www.oehha.ca.gov/prop65/pdf/estragf.pdf)
- 2- ESCOP Monographs. The Scientific Foundation of Herbal Medicinal Products, 2nd ed. Stuttgart, Thieme, 2003.
- 3- Fintelmann V, Weiss R: Lehrbuch der Phytotherapie, Aufl. Stuttgart, Hippokrates, 2002.
- 4- Merfort I, Schmidt E: Säuglings- und Kindertees – Pharmakologie und Anwendung; in Saller R, Feiereis H (Hrsg): Beiträge zur Phytotherapie. München, Marseille, 81–92, 1993.
- 5- De Vincenzi M, Silano M, Maialetti F, Scazzocchio B. Safety data review – Constituents of aromatic plants : II. Estragole *Fitoterapia* 71:725-729, 2000.
- 6- Miller EC, Swanson AB, Phillips DH, Fletcher TL, Liem A, Miller JA: Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. *Cancer Res* 43:1124– 1134, 1983.
- 7- Miller JA, Miller EC: The metabolic activation and nucleic acid adducts of naturally occurring carcinogens: Recent results with ethyl carbamate and the spice flavors safrole and estragole. *Br J Cancer* 48:1–15, 1983.
- 8- Wiseman RW, Miller EC, Miller JA, Liem A: Structure-activity studies of the hepatocarcinogenicities of alkenylbenzene derivatives related to estragole and safrole on administration to preweanling male C57BL/6J × C3H/HeJ F1 mice. *Cancer Res* 47:2275–2283, 1987.
- 9- European Commission Scientific Committee on Food: Opinion of the Scientific Committee on Food on estragole (1-Allyl-4-methoxybenzene). September 26, 2001.
- 10-<http://cms.herbalgram.org/expandedE/Fenneloil.html>

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11-[http://www.naturheilkunde.usz.ch/LehreUndForschung/Publikationen/Documents/Fennel%20tea%20in%20infancy\\_Poster\\_fi.07.pdf](http://www.naturheilkunde.usz.ch/LehreUndForschung/Publikationen/Documents/Fennel%20tea%20in%20infancy_Poster_fi.07.pdf)

12- Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (Foeniculum Vulgare) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. *Altern Ther Health Med.* 9:58-61, 2003.

Additional references:

<http://www.wellness.com/reference/herb/fennel-foeniculum-vulgare/references>

12-Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (*Foeniculum Vulgare*) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. *Altern Ther Health Med.* 9:58-61, 2003.

Additional references:

<http://www.wellness.com/reference/herb/fennel-foeniculum-vulgare/references>

## **Annex IV: Safety of the constituents of the formula**

EAFUS status

ASP 1707ANISE, OIL (PIMPINELLA ANISUM L.) 80077-0-182.203

ASP 2089FENNEL, COMMON (FOENICULUM VULGARE MILL.) 9770011- 182.103-0

ASP 2531PEPPERMINT, OIL (MENTHA PIPERITA L.) 80069-0-172.2304

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ASP - Fully up-to-date toxicology information has been sought.

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[Code of Federal Regulations]

[Title 26, Volume 6, Parts 500 to 599]

[Revised as of April 1, 1998]

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 582--**SUBSTANCES GENERALLY RECOGNIZED AS SAFE**--Table of Contents Subpart

A--General Provisions

Sec. 582.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates).

Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are generally recognized as safe for their intended use, within the meaning of section 409 of the act, are as follows:

Common name                      Botanical name of plant source

----- \*Anise.....

Pimpinella anisum L.

\*Fennel..... Foeniculum vulgare Mill.

\*Peppermint..... Mentha piperita L.