Health Canada Santé Canada

September 15, 2016

Notice

Our file number:

Revised Guidance Document: Acetaminophen Labelling Standard

The final version of the Health Canada Revised *Guidance Document - Acetaminophen Labelling Standard* is now available. Comments and suggestions received from the consultation between September to December 2015 on the draft version of the guidance were reviewed and considered in the finalization of this document. The labelling standard has been revised based on the outcome of the 2014 acetaminophen review which recommended that the label include stronger alcohol consumption-related warnings, the recommendation that a dosing device be included with children's liquid products and more safety information with regards to the product's content. A copy of the Summary Safety Review - Acetaminophen - Liver Injury can be obtained at the following link: http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/acetamino-eng.php.

This labelling standard replaces the October 28, 2009 *Acetaminophen Labelling Standard Guidance Document*. The updated labelling standard includes a Drug Facts Table that will provide safety information in an easy-to-read format and uses plain language, so that consumers can more easily identify products that contain acetaminophen, understand the risks of liver injury and use the products as directed. The table also includes alcohol-related directions and clearer identification of products that contain acetaminophen.

This final labelling standard is effective immediately for all submissions seeking a new market authorization. Holders of market authorizations for existing products are strongly encouraged to effect any necessary labelling changes as soon as possible by submitting an updated label for review via a Post-authorization Division 1 Change. By March 2018, Health Canada expects all products to comply with the new labelling standard and will take appropriate regulatory measures, as circumstances warrant, to deal with any products that remain on the market without updated labelling.

This standard should also be used to inform the labelling of products that contain acetaminophen in addition to other ingredients (other than caffeine and codeine as specified in the standard), but which would not be submitted to Health Canada under the Labelling Standard stream.

As with any Guidance Document or Labelling Standard, alternate approaches may be acceptable provided they are supported by adequate justification and data. In these cases, an application outside of the Labelling Standard should be submitted.

Should you have any questions or comments regarding the content of the guidance, please contact:

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GUIDANCE DOCUMENT
Acetaminophen Labelling Standard

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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre : *Ligne directrice : Norme d'étiquetage pour l'acétaminophène*

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. They also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. These alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1. INTRODUCTION

This labelling standard describes the requirements necessary to receive marketing authorization (a Drug Identification Number (DIN)) for non-prescription oral analgesics containing acetaminophen as a single ingredient and in combination with caffeine and/or with codeine. Preparations containing codeine for paediatric use are not acceptable under this labelling standard.

2. MEDICINAL INGREDIENTS

TABLE 1: Drug Medicinal Ingredients and Dosage

Medicinal ingredient preferred name	Dosage Units (adult ≥12years)[a]	Dosage Units (children <12 years)[b]	Specific Regulatory Requirement
Acetaminophen	325 mg	80mg/mL or 160 mg/5mL	• C.09.020 (1), (2) of the *Food and Drug Regulations (FDR)*; • A liquid dosage form is to be either of the children's standard dosage units per mL for drops, or per teaspoon (5 mL) for other liquid formulations. C.09.022 (4), (5); • An accurate measuring device shall be provided and must be capable of accurately delivering 0.5 millilitres of the children's drops. C.09.022 (6)
	500 mg		The label must state this is not a standard dosage unit.[c]
	650 mg		The label must state this is not a standard dosage unit.[c]
Caffeine	15 or 65 mg[d]	Not applicable	Acetaminophen and caffeine are acceptable in combination products. C.09.021 (1) of the *Food and Drug Regulations (FDR)*
Codeine[e]	8 mg (solid) 20 mg/30 mL (liquid)[e]	0 mg	May be combined with adult dosage of acetaminophen + 15 mg caffeine per dosage unit[f]

[a] Note that for a liquid dosage form, a standard adult dosage unit is 325 milligram per teaspoon (5 millilitres). C.09.022 (7).
[b] C.09.024 of the *Food and Drug Regulations.*
[c] C.09.022 (1),(2) of the *Food and Drug Regulations.*
[d] Codeine may be combined with Caffeine (15 milligram) and a dosage unit of acetaminophen. Caffeine at 65 milligram can be combined with a dosage unit of acetaminophen. Any other combination will be reviewed outside the labelling standard.
[e] Pediatric preparations containing codeine are not acceptable under this labelling standard.
[f] Section 36. (1) of the *Narcotic Control Regulations.*

3. PHARMACEUTICAL FORMS

3.1 Acceptable:

- Immediate release solid oral dosage forms such as tablets, caplets, capsules, chewable tablets, effervescent tablets, granules or powder for dissolution.
- Oral liquid formulations such as solutions, suspensions, syrups, drops, elixir.

3.2 Unacceptable:

- Modified dose release (e.g. liquid extended release, solid oral sustained release, bi-layer formulations or enteric coated products).
- Products that require evaluation of animal sourced ingredients (e.g. animal tissue based gelatin capsules, where a valid European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability or equivalent is not provided).
- Other dosage forms: e.g. chewable liquid filled capsule, powder dosage form intended for direct application to the mouth, thin strips, lollipops, popsicles/freezer pops, etc.

4. USES

To help prevent dosing errors, acetaminophen-containing products may not be concurrently labeled for:

- both adults and children (≥12 years) and children (<12 years); **OR**
- both infants (<2 years) and children (≥2 years).

4.1 Acceptable Indications

Pain reliever or fever reducer

Antipyretic:

- Reduces fever.

Analgesic:

Temporarily relieves mild to moderate aches and pains due to:

- headache / backache / migraine / sore throat
- arthritis or rheumatism
- pre-menstrual / menstrual cramps
- toothache / teething pain
- muscular sprains and strains
- common cold and flu
- immunization

4.2 Unacceptable Indications

The following indications for acetaminophen products are excluded and would require a review outside of the labelling standard. These include but are not limited to:

- severe pain;
- treatment of arthritis, rheumatism;
- rheumatic fever;
- treatment of migraine and associated symptoms (nausea, sensitivity to light and/or sound, etc.);
- neuralgia;
- pain relief adjuvant/enhancer;
- mental alertness/prevents drowsiness/stimulant;
- enhancement of motor/cognitive performance;
- sleep aid;
- sedation.

5. DOSAGE DIRECTIONS

5.1 Dosage for Adults and Children 12 years and older

TABLE 2: Dosages for Adults and Children 12 years and older[g]

Dosage Unit[g]	Single Dose	Dose Interval[h]	Maximum[i] Daily Dose	Maximum Daily Dosage Units
325 mg	1 or 2 x 325 mg	every 4 - 6 hours	4000 mg	12
500 mg[j]	1 or 2 x 500 mg	every 4 - 6 hours	4000 mg	8
650 mg	1 x 650 mg	every 4 - 6 hours	4000 mg	6

[g] C.01.024, C.01.025, C.09.022(1),(2) of the *Food and Drug Regulations*. All other recommended doses or dosage units fall outside the scope of this labelling standard.

[h] AHFS® 2016; Hersh et al, 2000; Moore et al, 2008; Repchinsky et al., 2002.

[i] C.01.021 of the *Food and Drug Regulations.*

[j] **Acetaminophen and caffeine:**

- *Single dose (1 or 2 dosage units)***:** 65 milligrams caffeine in combination with 500 milligrams acetaminophen every 4 - 6 hours (Hersh et al, 2000; Ali et al, 2007; Sawynok J and Yaksh TL, 1993; Zhang Wei-Ya, 2001).
- *Maximum daily dose***:** 520 milligrams caffeine/day.

Dosage directions for adults and children 12 years and older must state:

a) For all doses:
- Take 1 (*caplet/tablet/etc.*) every 4-6 hours.

b) For doses where more than 1 dosage unit is recommended (e.g. 325mg and 500mg strengths):
- If pain or fever does not improve after one (1) (*caplet/tablet/etc.*), take two (2) (*caplets/tablets/etc.*) at next dose.

c) For all doses: **Do not** take more than 4000 mg (or X tablets/mL/doses) in 24 hours.

5.2 Dosages for Children under 12 years

The age-related dosing is provided as per the *Food and Drug Regulations* (C.01.024) for use when the weight of a child is unknown. The weight-related dosing is also provided.

TABLE 3: Dosages for Children Under 12 years of Age[k,l,m]

Age (Years)	Single Dose				Maximum Daily Dose		
	mg	**X 80 mg**	**X 160 mg**	**X 325 mg**	**mg**	**X 80 mg**	**X 160 mg**
11 to under 12	480	6	3	1 ½	2400	30	15
9-10	400	5	2 ½	1 ¼	2000	25	12 ½
6-8	320	4	2	1	1600	20	10
4-5	240	3	1 ½		1200	15	7½
2-3	160	2	1		800	10	5
Age (Months)							
12-23	120	1 ½			600	7 ½	
4-11	80	1			400	5	
0-3	40	½			200	2½	

[k] C.01.024 of the *Food and Drug Regulations*.
[l] **Dosing interval:** Every 4-6 hours. (AHFS, 2016; Repchinsky et al., 2002)
[m] Solid dosage forms, for which half (1/2) or quarter (1/4) doses are recommended, must be adequately scored to ensure proper dosage.

TABLE 4: Dosages for Children based on Weight[n]

Body Weight		Single Dose (mg)	Maximum Daily Dose (mg)
Pounds (lbs)	Kilograms (kg)		
72-95	32.0-43.9	480	2400
60-71	27.0-31.9	400	2000
48-59	22.0-26.9	320	1600
36-47	16.0-21.9	240	1200
24-35	11.0-15.9	160	800
18-23	8.0-10.9	120	600
12-17	5.5-7.9	80	400
6-11	2.0-5.4	40	200

Dosage directions for children under 12 years of age must state:

a) For all doses: **Do not** take more than XX mg (or X tablets/mL/doses) in 24 hours.

5.3 Dosage Considerations

1. The quantitative declaration of the medicinal ingredients on any panel of the inner and outer labels should be prominently displayed and should be further identified by the therapeutic class or indication listed under **Section 4.1**, e.g.: "Medicinal Ingredient: Acetaminophen (analgesic/antipyretic) 325 mg"; "Medicinal Ingredient: Acetaminophen (pain reliever/fever reducer) 325 mg".

2. The labels should declare the recommended single and maximum daily dose, as well as the dosing interval for the product. Maximum daily dose may be expressed as: "Do not take more than XX mg (or X tablets/mL/doses) in 24 hours."

3. For liquid formulations, it is recommended that a dosing device be provided and the following statement should be included with the directions for use: "Use only the measuring device provided."

4. The dose information should be expressed in units of measure that correspond to the calibration of the dose delivery device, and include instructions that are consistent with the measuring device.

[n] Temple, 1983 and 2013.

5.4 Combinations

Applicants should apply outside of the labelling standard if they wish to combine acetaminophen with medicinal ingredient(s) other than caffeine and/or codeine.

Please note that all labelling requirements for acetaminophen in this LS also applies to products combining acetaminophen with any other medicinal ingredient.

6. WARNINGS

6.1 For outer and inner labels of all acetaminophen products

- **KEEP OUT OF THE REACH OF CHILDREN.** C.01.029 (1)[o,p]
- This package contains enough drug to seriously harm a child (if greater than 3.2 grams of acetaminophen in the package). C.01.029 (2)(c)[o, p]
- **DO NOT USE** with other drugs containing **acetaminophen**. If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.
- **DO NOT USE** if you are allergic to acetaminophen or any other ingredient in this product

- **Liver warning** [q] (should be **bold** font type and in red text): This product contains acetaminophen. Maximum daily dose is X <tablets/caplets> (XX mg) in 24 hours[r]. **Severe or possibly fatal liver damage** may occur if you take:
  - more than the recommended dose in 24 hours;
  - with other drugs containing acetaminophen;
  - while drinking three (3) or more alcoholic drinks every day (*for adult use products only*).

  Symptoms of liver damage may include:

  - yellowing of the skin/eyes, dark urine;
  - sweating, nausea, vomiting, stomach pain;
  - unusual tiredness, and/or loss of appetite.

[o] Must be preceded by a prominently displayed symbol that is octagonal in shape, conspicuous in colour and on a background of a contrasting colour. C.01.029 (3)

[p] Above highlighted items do not apply if the product is in an effervescent or powder form; or packaged in a non-reclosable package containing not more than two adult standard dosage units per package. C.01.031.2(c),(d),(f)

[q] Health Canada, Summary Safety Review – Acetaminophen – Liver Injury, July 9, 2015.

[r] C.09.011 (b), C.01.024 (3)(b) of the *Food and Drug Regulations.*

- **Allergy alert:** acetaminophen may cause serious skin reactions. Symptoms may include:
  - skin reddening, blisters, rash.

If any of the above noted symptoms occur, stop use and seek medical help right away.

Ask a doctor before use if you:

- have a liver or kidney disease.

Ask a doctor or pharmacist before use if you:

- are taking Warfarin-containing blood thinning drugs;
- are pregnant or breast feeding.

Stop use and ask a doctor if:

- pain lasts for more than five (5) days [s];
- fever lasts for more than three (3) days [r].

- **In Case of Overdose:** Call a Poison Control Centre or get medical help right away. Quick medical attention is critical even if you do not notice any signs or symptoms.

6.2 Additional Warnings for combinations with 65 mg caffeine

- Avoid other caffeine containing products. Too much caffeine may cause rapid heart rate, nervousness or sleeplessness.
- Ask a doctor or pharmacist before use if you have high blood pressure, glaucoma, or overactive bladder syndrome.

6.3 Additional Warnings for combinations with codeine

- **DO NOT USE if you**:
  - are allergic to codeine or other opioids;
  - are in your last trimester of pregnancy or breast-feeding. Codeine may cause serious harm to a breastfed baby;
  - have difficulty breathing, have asthma, chronic lung disease or other chronic breathing problems;
  - have suffered head injury;

[s] C.09.011(a) of the *Food and Drug Regulations.*

- are at risk of blocked intestines or constipation;
- suffer from seizures.

- The following warning must appear conspicuously on the principal display panel of the inner and outer label:

"This preparation contains codeine and should not be administered to children except on the advice of a physician, dentist or nurse practitioner." (Section 36(1) of the *Narcotic Control Regulations*).

Ask a doctor before use if you:

- are taking other medications that can make you sleepy or less alert, for example: narcotic analgesics, sedating antihistamines; or anti-depressants, other prescription drugs, three (3) or more alcoholic drinks every day; or you have recently had surgery under general anaesthesia.

Stop use and ask a doctor if you:

- feel sedated or drowsy, confused, have shallow breathing or have severe constipation.

7. DRUG FACTS TABLE: RECOMMENDED (NOT MANDATORY)[t]

Drug Facts

Active ingredient (in each dosage unit) **Purpose**
Acetaminophen XX mg…….…..…….…..…. Pain reliever, fever reducer

Uses ● Reduces fever ● Temporarily relieves mild to moderate aches and pain due to ▪ headache ▪backache ▪migraine ▪sore throat ▪arthritis or rheumatism ▪ pre-menstrual/menstrual cramps ▪ muscle sprains and strains ▪ toothache / teething pain ▪common cold and flu ▪immunization

Warnings

Liver warning: Acetaminophen may cause **severe or possibly fatal liver damage** if you take ▪more than the recommended dose in 24 hours ▪with other drugs containing acetaminophen ▪ while drinking 3 or more alcoholic drinks every day (adult products only) Symptoms of liver damage may include ▪yellow skin or eyes ▪dark urine ▪sweating ▪nausea ▪vomiting ▪stomach pain ▪unusual tiredness ▪loss of appetite

Allergy alert: Acetaminophen may cause serious skin reactions. Symptoms may include ▪skin reddening ▪ blisters ▪rash **If any of the above noted symptoms occur, stop use and seek medical help right away.**

Do not use ▪with any other drug containing **acetaminophen** ▪if you are allergic to acetaminophen or any other ingredient in this product. If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.

Ask a doctor before use if you have liver or kidney disease.

Ask a doctor or pharmacist before use if you take the blood thinning drug warfarin.

Stop use and ask a doctor if ▪pain lasts for more than 5 days ▪fever lasts more than 3 days

If pregnant or breastfeeding, ask a healthcare professional before use.

Keep out of reach of children. This package contains enough drug to seriously harm a child (if greater than 3.2 grams of acetaminophen in the package).
In case of overdose, call a Poison Control Centre or get medical help right away. Quick medical attention is critical even if you do not notice any signs or symptoms.

Directions ▪Do not take more than directed (see liver warnings)
Adults and children 12 years and over: ▪take 1(tablet/caplet/etc.) every 4 to 6 hours ▪if pain or fever does not respond to 1 (tablet/caplet/etc.), take 2 (tablets/caplets/etc.) at next dose ▪do not take more than X mg (xx tablets) in 24 hours

Other information ▪ (if no information here, delete this heading)

Inactive ingredients <List all NMIs>

Questions? Call 1-XXX-XXX-XXXX (or other contact information)

[t] The regulatory amendment for a Fact Table for non-prescription drug products would come into force three years after the day of registration in *Canada Gazette* Part II (June 13, 2017).
http://gazette.gc.ca/rp-pr/p2/2014/2014-07-02/html/sor-dors158-eng.php
Specifications for Drug Facts table can be found under section 2.4.4 of the guidance document: *Good Label and Package Practice Guide for Non-prescription Drugs and Natural Health Products*.
http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2016-label-package-practices-pratiques-etiquetage-emballage-non/index-eng.php

8. OTHER REQUIREMENTS

8.1 For all products

Declaration of acetaminophen on the product label:

- **Principal display panel:**
  - For single ingredient products:
    - "**Contains Acetaminophen**" should appear in **bold** font type, font size 10 and in **red** text with a white background in the top right corner of the label.
  - For multi-ingredient products:
    - "**Contains Acetaminophen and other Ingredients**" should appear in **bold** font type and font size 10 in the top right corner of the label. In addition, the text for "**Contains Acetaminophen**" should appear in **red** with a white background.
  - For small package sized products:
    - Consideration will be given for products with small package size. However, the text for "**Contains Acetaminophen**" should appear prominently in **bold** font type in **red** with a white background in the top right corner of the label.

Declaration of acetaminophen on the Drug Facts Table:

- **Acetaminophen** should appear in **bold** font type and highlighted.

Declaration of ingredients for all products:

Section C.01.004 of the *Food and Drug Regulations* indicates that for single ingredient products and/or products for which a compendial standard exists, the following must be shown on the inner and outer labels:

- the proper name on the principal display panel immediately preceding or following the brand name in a font size not less than half (1/2) the size of the brand name.
- a quantitative list of the medicinal ingredients by their proper names, or common names if they have no proper names.
- a qualitative list of non-medicinal ingredients clearly distinguished from the medicinal ingredients.

Health Canada's **Guidance Document: Labelling of Pharmaceutical Drugs for Human Use** should be consulted for applicable labelling requirements.

- At least one of the package sizes available for sale must be provided in a child resistant package and the outer label of all containers that are not child resistant shall carry a statement that the drug is also available in a child resistant package. C.01.031(a)(ii),(b)[p]

- For adult use only products containing more than two (2) or three (3) times the standard adult dosage unit or for products that recommend dosages in excess of 650 mg per single dose, and/or 4 grams per day, the label must state that the product is to be used only on the advice of a doctor. (C.01.025)

- **For children's use only products**:
    - the drug is to be packaged in a child resistant container. C.01.031(a)(i);

    - the package size is limited to no more than 1.92 grams in the 80 mg dosage units or 3.2 grams in the 160 mg dosage units. C.01.037(c)(d);

    - the word "**Children**" or "**Infants**" must appear in **bold** font type on the principal display panel of all labels to help prevent dosing errors.

Legibility:

Although no specific type size is mentioned in the *Food and Drug Regulations*, Section A.01.016 specifies that all information required to appear on a label must be:

- Clearly and prominently displayed, and
- Readily discernible to the purchaser or consumer under the customary conditions of purchase and use.

A person with normal vision, or those with corrective glasses that restore normal vision, should be able to read the information without straining. The colour, contrast, the position, and the spacing of the information are all to be taken into consideration in complying with these requirements.

8.2 For products containing codeine

- The active ingredients of products containing codeine must appear conspicuously on the principal display panel of the inner and outer label (Section 36(1) of the *Narcotic Control Regulations*).
- The inner and outer labels shall show on the upper left quarter of the principal display panel of the label, the symbol "N" in a colour contrasting with the rest of the label or in type not less than half (1/2) the size of any other letters used thereon.

9. SPECIFICATIONS

This labelling standard describes those requirements that are specific to this class of drug.

- Products must comply with the requirements in the *Food and Drugs Act* and associated Regulations. It is also noted that all products are subject to Part C, Division 2 of the *Food and Drug Regulations*.

- All ingredients (medicinal and non-medicinal) and finished product specifications must meet or exceed the standards described in the publications referred to in Schedule B of the *Food and Drugs Act*, or equivalent standards.

- Where no Schedule B monograph exists for the finished product's dosage form, specifications should be similar to those of a comparable compendial dosage form demonstrating the product's identity, potency, purity and quality.

- Finished product specifications should include tests for identification and an assay with suitable limits for the medicinal ingredient(s). The specifications for all dosage forms should include a description of the dosage form, including organoleptic properties as well as physico-chemical testing (e.g. pH, specific gravity, viscosity), appropriate to the dosage form. Where antimicrobial preservatives are added, an assay with suitable limits should be included. Antimicrobial preservative effectiveness should be determined in order to establish that the product is capable of resisting microbial contamination.

- Any change to the manufacturing process that impacts the safety and efficacy of the ingredients, such as the use of novel technology (e.g. nanotechnology), requires supporting data and will be reviewed outside the labelling standard.

10. NON-MEDICINAL INGREDIENTS

Non-medicinal ingredients must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in that database, the *Food and Drug Regulations* (FDR), and/or the *Herbs used as Non-medicinal Ingredients in Nonprescription Drugs for Human Use*, when relevant.

11. SPECIAL NOTES

Codeine, although meeting the definition of a natural health product under Schedule 1 of the NHPR, is excluded under Schedule 2 of the NHPR since it is subject to the *Controlled Drugs and Substances Act*.

Products making different dosing recommendations or using different dosage units of acetaminophen other than those listed in Tables 1-4 will require an application to be filed outside the labelling standard. Sufficient supporting data, demonstrating the safe and effective use of such a product, will need to be submitted for assessment.

Submissions for combinations of various strengths of acetaminophen, codeine and/or caffeine may require additional supporting data to demonstrate that the combination has a therapeutic advantage over existing products and that the enhanced benefit justifies the potential increased risk that may be associated with the new combination (Zhang WY and Po AL, 1996; Mitchell et al, 2008; Martell BA, 2007). As such, combinations other than those listed under section 2 will require an application to be filed outside the labelling standard.

12. REFERENCES

1. American Hospital Formulary Service®. AHFS Drug Information® 2016. Published by Authority of the Board of the American Society of Health-System Pharmacists®, Bethesda, Maryland.

2. Ali Z, Burnett I, Eccles R, North M, Jawad M, Jawad S, Clarke G, Milsom I. Efficacy of a paracetamol and caffeine combination in the treatment of the key symptoms of primary dysmenorrhea. Current Medical Research and Opinions 2007;23(4):841-851.

3. George R. Aronoff et al. editor. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and children, 5th edn. Portland, OR, American College of Physicians; (2007).

4. Daniel L. Krinsky, Stefanie P. Ferreri et al. editor. Handbook of Nonprescription Drugs. 18th ed. Washington, District of Columbia: American Pharmaceutical Association; 2015.

5. Bradley JD, Brandt KB, Katz BP, Kalasinski LA, Ryan SI. Comparison of an Anti-inflammatory Dose of Ibuprofen, An Analgesic Dose of Ibuprofen, and Acetaminophen in the Treatment of Patients with Osteoarthritis of the Knee. N Eng J Med 1991;325:87-91.

6. Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ. Lifetime nonnarcotic analgesic use and decline in renal function in women. Archives of Internal Medicine. 2004;164(14):1519-24.

7. Deiner HC, Pfaffenrath V, Pageler L, Peil H, Aicher B. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalgia 2005;25:776-787.

8. Draganov P, Durrence H, Cox C, Reuben A. Alcohol-acetaminophen syndrome: Even moderate social drinkers are at risk. Postgraduate Medicine 2000;107(1):189-195.

9. European Medicines Agency: Codeine-containing medicinal products for the treatment of cough or cold in paediatric patients; April 24, 2015 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products_for_the_treatment_of_cough_and_cold_in_paediatric_patients/human_referral_prac_000039.jsp&mid=WC0b01ac05805c516f

10. Food and Drug Administration (FDA). Federal Register: April 29, 2009 (Vol 74. Number 81): Final Rule. 21 CFR parts 201. Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Monograph.

11. Food and Drug Administration (FDA). CFR 21, Part 201.63. (Vol 4, Revised as of April 1, 2015). Labelling Requirements for Over-The-Counter Human Drugs; Pregnancy/breast-feeding warning.

12. *Food and Drugs Act and Regulations*: http://laws-lois.justice.gc.ca/eng/acts/f-27/, and http://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html.

13. Fontana J, Quallich LG. Acute Liver Failure. Current Opinion in Gastroenterology 2001;17(3):291-298.

14. Gashe Y, Daali Y, Fathi M, Chippe A, Cottini S, Dayer P, Desmueles J. Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism. New England Journal of Medicine 2004;351:2827-31.

15. Gaziano MJ, Gibson MC. Potential for Drug-Drug Interactions in Patients Taking Analgesics for Mild-to-Moderate Pain and Low-Dose Aspirin for Cardioprotection. The American Journal of Cardiology, 2006;97(9A):23E-29E.

16. Guidance for Industry: Product Monograph. Health Canada, June 01, 2014.

17. Health Canada Advisory, October 8, 2008. Use of Codeine Products by Nursing Mothers. http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/13255a-eng.php

18. Health Canada Guidance Document, June 30, 2016. Good Label and Package Practices Guide for Non-prescription Drugs and Natural Health Products http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2016-label-package-practices-pratiques-etiquetage-emballage-non/index-eng.php

19. Health Canada Summary Safety Review - Acetaminophen - Liver Injury, July 9, 2015. http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/acetamino-eng.php.

20. Hersh EV, Moore PA, Ross G L. Over-The-Counter Analgesics and Antipyretics: A Critical Assessment. Clinical Therapeutics 2000; 22(5):500-548.

21. Hersh EV, Pinto A, Moore PA. Adverse drug interactions involving common prescription and over-the-counter analgesic agents. Clinical Therapeutics 2007;29 Suppl:2477-97.

22. Information for Healthcare Professionals: Use of Codeine Products in Nursing Mothers. FDA Alert August 17, 2007.U.S. Food and Drug Administration.

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124889.htm

23. Kaplowitz N. Acetaminophen Hepatotoxicity: What Do We Know, What Don't We Know and What Do We Do Next? Hepatology 2004;23–26. http://onlinelibrary.wiley.com/doi/10.1002/hep.20312/full

24. Koniman R, Chan Y H, Tan T N, Van Bever H P. A matched patient-sibling study on the usage of paracetamol and the subsequent development of allergy and asthma Pediatric Allergy and Immunology, 2007;18:128-134.

25. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder S J. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006;368:704.

26. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, Reisch JS, Schiødt FV, Ostapowicz G, Shakil AO, Lee WM. Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005 Dec;42(6):1364-72.

27. Lee WM. Acetaminophen Toxicity: Changing Perceptions on a Social/Medical Issue. Hepatology, 2007 Oct;46(4):966-70.

28. Martell BA, Systemic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy and Association with Addiction. Annals of Internal Medicine (Review) 2007;146:116-127.

29. McQuay HJ, Moore RA. An Evidence-based Resource For Pain Relief. Oxford University Press, 2002. p. 58-77.

30. Medicines and Healthcare Products Regulatory Agency, **Annual Report and Accounts** 2004/05. Making an effective contribution to public health. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/228822/0719.pdf

31. Meyer D, Tobias JD. Adverse Effects Following the Inadvertent Administration of Opioids to Infants and Children. Clinical Pediatrics, 2005 July/August;499-503.

32. Migliardi JR, Armellino JJ, Friedman M, Gillings DB, Beaver WT. Bristol-Myers Products, Hillside, New Jersey 07205. Clin Pharmacol Ther. 1994 Nov;56(5):576-86.

33. Mitchell A, van Zanten SV, Inglis K, Porter G. A Randomized Controlled Trial Comparing Acetaminophen plus Ibuprofen versus Acetaminophen plus Codeine plus Caffeine after Outpatient General Surgery. Journal of American College of Surgeons. 2008 March;206(3):472-479.

34. Moore A, Collins S, Carroll D, McQuay H, Edwards J. Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. The Cochrane Collaboration. Published by John Wiley & Sons Ltd., 2008.

35. *Narcotic Control Regulations*: http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._1041/FullText.html.

36. Prescott LF. Paracetamol (Acetaminophen): A Critical Bibliographic Review. London: Taylor and Francis Ltd. 1996.

37. Renner B, Clarke G, Grattan T, Beisel A, Mueller C, Werner U, Kobal G, Brune K. Caffeine Accelerates Absorption and Enhances the Analgesic Effect of Acetaminophen. Pharmacokinetics and Pharmacodynamics Journal of Clinical Pharmacology, 2007; 47:715-726. http://onlinelibrary.wiley.com/doi/10.1177/0091270007299762/full

38. Repchinsky Carol, editor-in-chief. Patient Self-Care: Helping patients make therapeutic choices. 2nd ed. Ottawa: Canadian Pharmacists Association; 2010.

39. Sawynok J and Yaksh TL. Caffeine as an Analgesic Adjuvant: A Review of Pharmacology and Mechanisms of Action. Pharmacological Reviews.1993;45(1):43-85.

40. Temple A. Pediatric Dosing of Acetaminophen. Pediatric Pharmacology, 1983;3: 321-327.

41. Temple AR, Benson GD, Zinsenheim JR, Schweinle JE. Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel-Group Trial of the Long-Term (6-12 months) Safety of Acetaminophen in Adult Patients with Osteoarthritis. Clinical Therapeutics. 2006;28(2):222-235.

42. Temple AR, Temple BR, Kuffner KE. Dosing and Antipyretic Efficacy of Oral Acetaminophen in Children. Clinical Therapeutics. 2013;28(9):1361-1375.

43. United States Food and Drug Administration: Codeine Cough-and-Cold Medicines in Children: Drug Safety Communication - FDA Evaluating Potential Risk of Serious Side Effects, July 1, 2015. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm453379.htm

44. United States Food and Drug Administration: FDA Warning on Codeine Use by Nursing Mothers, August 17, 2007. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108968.htm

45. Zhang Wei-Ya. A Benefit-Risk Assessment of Caffeine as an Analgesic Adjuvant. Drug Safety, 2001;24(15):1127-1142. http://link.springer.com/article/10.2165%2F00002018-200124150-00004

46. Zhang WY, Po AL. Analgesic Efficacy of paracetamol and its combination with codeine and caffeine in surgical pain a meta-analysis. Journal of Clinical Pharmacy and Therapeutics, 1996;21:261-282. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2710.1996.tb01148.x/pdf

47. Zimmerman H J, Maddrey WC. Acetaminophen (Paracetamol) Hepatoxicity With Regular Intake of Alcohol: Analysis of Instances of Therapeutic Misadventure. Hepatology 1995;22(3):767-772.