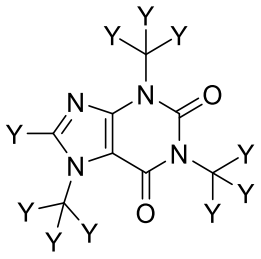
($t_{1/2}$), and rapid clearance, mainly by hepatic cytochrome P450 (CYP450) demethylation to afford paraxanthine, theobromine, and theophylline. In other words, ingestion of caffeine results in a large "spike" in caffeine plasma concentration (*i.e.*, large C_{max}) shortly after caffeine ingestion (*i.e.*, short T_{max}) followed by a "crash" in caffeine plasma concentration due to rapid metabolism and clearance. It is believed that the magnitude of this "spike" and the rapidity of this "crash" are at least partially responsible for the aforementioned adverse effects. Therefore, one approach to mitigate these adverse effects is to develop compounds and compositions that harness the positive attributes of caffeine without the negative effects, that is, with pharmacokinetic profiles exhibiting lower C_{max} values, longer half-life, and/or longer T_{max} values than caffeine.

SUMMARY

[0004] The present disclosure relates to compositions (*e.g.*, pharmaceutical compositions, nutraceutical compositions, foods, beverages, cosmetic compositions, diet supplements) comprising deuterated caffeine. In certain examples, the composition is suitable for oral administration. In certain examples, the composition is suitable for intravenous (IV) administration. In certain examples, the composition is suitable for topical administration. In certain examples, the composition is suitable for delivery to the lungs. In certain examples, the composition is administered using an electronic cigarette or other vaping device, a nebulizer, a pressurized metered dose inhaler (pMDI), or a dry powder inhaler (DPI). In certain examples, the composition is a solid dose composition (*e.g.*, tablet, capsule, granule, powder, sachet, or chewable), solution, gel, suspension, emulsion, shampoo, conditioner, cream, foam, gel, lotion, ointment, transdermal patch, tincture, or paste. Also provided herein are kits containing the compositions and instructions for use. Further provided herein are use of the compositions described herein for treating a disease, preventing a disease, treating a condition, and/or preventing a condition.

[0004a] In one aspect of the present disclosure, there is provided a beverage, food product, ~~pharmaceutical composition,~~ nutraceutical composition, or cosmetic composition comprising a compound of Formula (**I**):



(**I**),

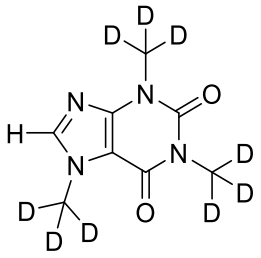
or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine ranges from 25% to 100%.

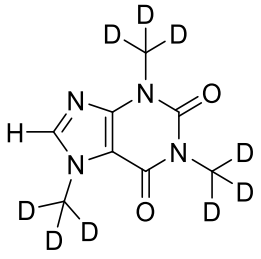
[0004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising compound (**14**):



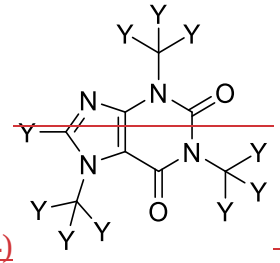
(**14**),

or a pharmaceutically acceptable salt thereof.

[~~0004b~~0004c] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein or a nutraceutical composition disclosed herein; or ~~a compound of Formula (I)~~compound (**14**):



(**14**)



~~(I)~~,

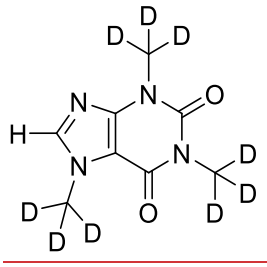
or a pharmaceutically or nutraceutically acceptable salt thereof;

~~wherein each Y is independently hydrogen or deuterium; and~~

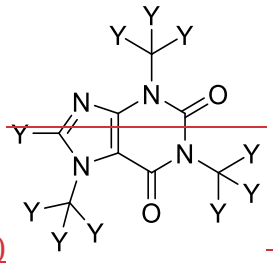
~~at least one Y is deuterium;~~

in the manufacture of a medicament for ~~increasing energy levels,~~ treating obesity, ~~causing weight loss, increasing metabolic rate, reducing appetite, increasing energy expenditure, increasing urine output, increasing sodium excretion,~~ reducing edema, treating a pain disorder, treating apnea, treating hypotension, treating an encephalopathy, treating aneurological or psychiatric disorder, or treating an inflammatory disorder in a subject.

[~~0004c~~0004d] In a further aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein or a nutraceutical composition disclosed herein; or ~~a compound of Formula (I)~~compound (**14**):



(**14**)



~~(I)~~,

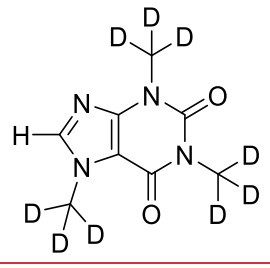
or a pharmaceutically or nutraceutically acceptable salt thereof;

~~wherein each Y is independently hydrogen or deuterium; and~~

~~at least one Y is deuterium;~~

for use in therapy.

[0004e] In a further aspect of the present disclosure, there is provided a method of increasing energy levels, causing weight loss, increasing metabolic rate, reducing appetite, increasing energy expenditure, increasing urine output, or increasing sodium excretion, the method comprising administering to the subject a composition comprising of compound (**14**):



(**14**)

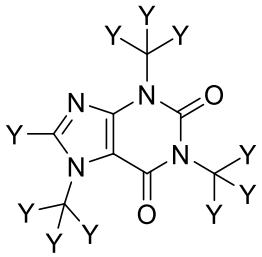
or a pharmaceutically or nutraceutically acceptable salt thereof.

[0005] The compositions described herein comprise deuterated caffeine (*i.e.*, wherein at least one of the hydrogen atoms of caffeine is replaced with deuterium). In certain examples, the composition comprises a compound of Formula (**I**):

CLAIMS

What is claimed is:

1. A beverage, food product, ~~pharmaceutical composition,~~ nutraceutical composition, or cosmetic composition comprising a compound of Formula (**I**):



(**I**),

or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

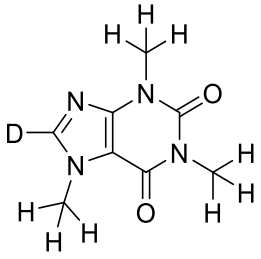
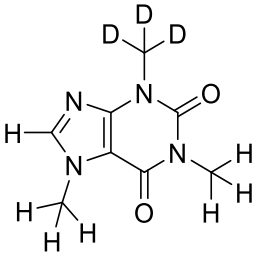
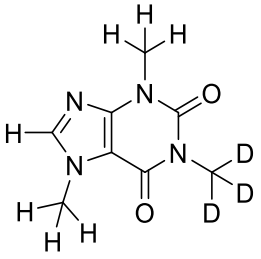
wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine ranges from 25% to 100%.

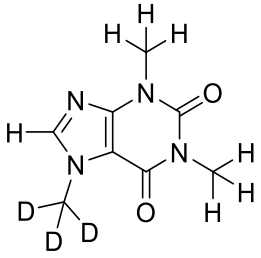
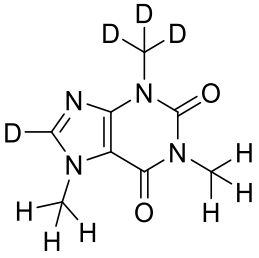
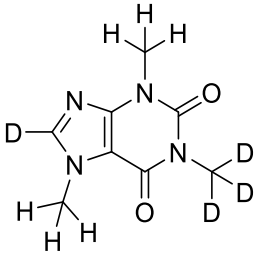
2. A beverage according to claim 1.

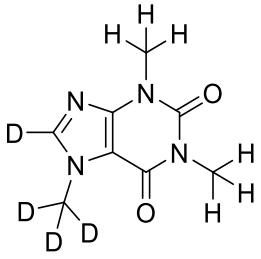
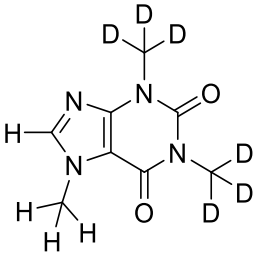
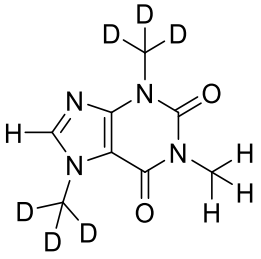
3. A food product according to claim 1.

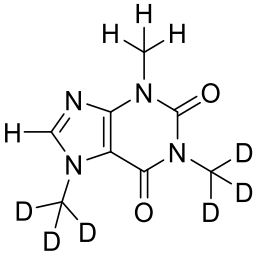
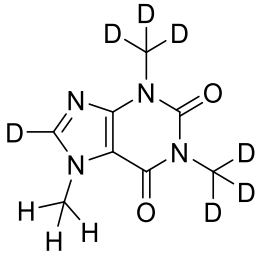
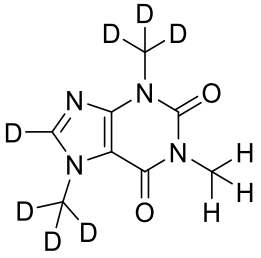
4. The beverage, food product, ~~pharmaceutical composition,~~ nutraceutical composition, or cosmetic composition of any one of claims 1-3, wherein at least three instances of Y are deuterium.

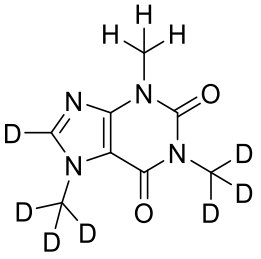
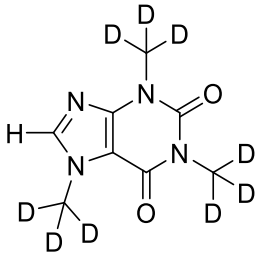
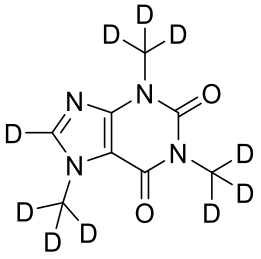
5. The beverage, food product, ~~pharmaceutical composition,~~ nutraceutical composition, or cosmetic composition of any one of claims 1-4, wherein the compound is selected from the group consisting of:


(**1**);

(**2**);

(**3**);


(**4**);

(**5**);

(**6**);

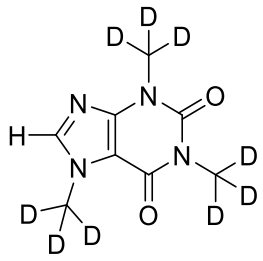

(**7**);

(**8**);

(**9**);


(**10**);

(**11**);

(**12**);


(**13**);

(**14**);

(**15**);

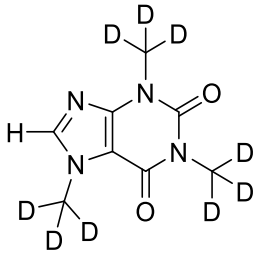
or a pharmaceutically or nutraceutically acceptable salt thereof.

6. The beverage, food product, ~~pharmaceutical composition,~~ nutraceutical composition, or cosmetic composition of any one of claims 1-4, wherein the compound is



(**14**), or a pharmaceutically or nutraceutically acceptable salt thereof.

7. A pharmaceutical composition comprising compound (**14**):



(**14**), or a pharmaceutically acceptable salt thereof.

~~7~~8. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims 1-6 or the pharmaceutical composition of claim 7, further comprising a pharmaceutically or nutraceutically acceptable carrier.

~~8~~9. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims ~~1-7~~1-6 and 8 or the pharmaceutical composition of claim 8 or 9, further comprising an additional agent.

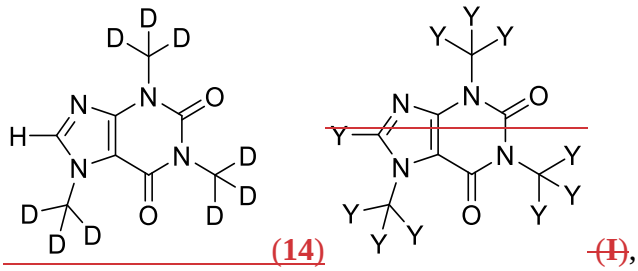
~~9~~10. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims ~~1-8~~1-6, 8 and 9 or the pharmaceutical composition of any one of claims 7-9, comprising ~~about~~ 1 mg to ~~about~~ 200 mg of the compound ~~of Formula (I)~~, or a pharmaceutically or nutraceutically acceptable salt thereof.

~~10~~11. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims ~~1-8~~1-6, 8 and 9 or the pharmaceutical composition of any one of claims 7-9, comprising ~~about~~ 1 mg/ml to ~~about~~ 25 mg/ml of the compound ~~of Formula (I)~~, or a pharmaceutically or nutraceutically acceptable salt thereof.

~~11~~12. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims 1-~~10~~6 and 8-11 or the pharmaceutical composition of any one of claims 7-11, wherein the percentage of the amount of the compound ~~of Formula (I)~~, or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine ranges from ~~about 10~~25% to ~~about~~ 99%.

13. The beverage, food product, nutraceutical composition, or cosmetic composition of any one of claims 1-6 and 8-11 or the pharmaceutical composition of any one of claims 7-11, wherein at least 99% of the total amount of caffeine in the composition is compound (**14**).

~~12~~14. Use of a pharmaceutical composition of any one of claims 7-13 or a nutraceutical composition of any one of claims ~~1-11~~1-6 and 8-13; or ~~a compound of Formula (I)~~compound (**14**):



(14) ~~(I)~~,

or a pharmaceutically or nutraceutically acceptable salt thereof;

~~wherein each Y is independently hydrogen or deuterium; and~~

~~at least one Y is deuterium;~~

in the manufacture of a medicament for ~~increasing energy levels,~~ treating obesity, ~~causing weight loss, increasing metabolic rate, reducing appetite, increasing energy expenditure, increasing urine output, increasing sodium excretion,~~ reducing edema, treating a pain disorder, treating apnea, treating hypotension, treating an encephalopathy, treating a neurological or psychiatric disorder, or treating an inflammatory disorder in a subject.

~~13~~15. The use of claim ~~12~~14, wherein side effects are reduced relative to the administration of caffeine at an equivalent dose.

~~14~~16. The use of claim ~~13~~15, wherein the side effect is anxiety, insomnia, gastrointestinal issues, rhabdomyolysis, addiction, hypertension, rapid heart rate, atrial fibrillation, fatigue, irritability, nervousness, restlessness, nausea, or muscle tremors.

~~15~~17. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims ~~1-11~~1-6 and 8-13, or the pharmaceutical composition of any one of claims 7-13, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the maximum plasma concentration (C_{max}) of the compound ~~of Formula (I)~~ after administration is lower than that of non-isotopically enriched caffeine at an equivalent dose.

~~16~~18. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims ~~1-11~~1-6 and 8-13, or the pharmaceutical composition of any one of claims 7-13, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the time of maximum plasma concentration (T_{max}) of the compound ~~of Formula (I)~~ after administration is longer than that of non-isotopically enriched caffeine at an equivalent dose.

~~17~~19. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims ~~1-11~~1-6 and 8-13, or the pharmaceutical composition of any one of claims 7-13, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the plasma half-life ($t_{1/2}$) of the compound ~~of Formula (I)~~ after administration is longer than that of non-isotopically enriched caffeine at an equivalent dose.

20. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of claim 19, wherein the compound is compound (**14**), and wherein the plasma half-life ($t_{1/2}$) of the compound after administration is at least 300% longer than that of non-isotopically enriched caffeine at an equivalent dose.

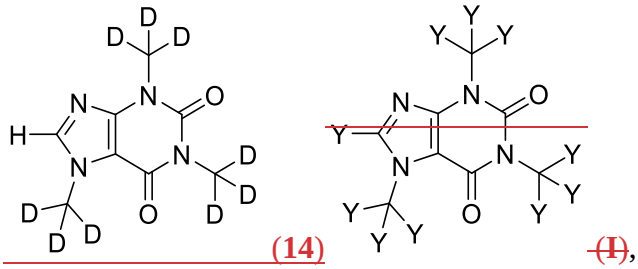
~~18~~21. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims ~~1-11~~1-6 and 8-13, or the pharmaceutical composition of any one of claims 7-13, wherein the beverage, food product, pharmaceutical

composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the maximum concentration (C_{max}) of the compound ~~of Formula (I)~~ in the central nervous system (CNS) of the subject after administration is lower than that of non-isotopically enriched caffeine at an equivalent dose.

~~19~~22. The beverage, food product~~, pharmaceutical composition~~, nutraceutical composition, or cosmetic composition of any one of claims ~~1-11~~1-6 and 8-13, or the pharmaceutical composition of any one of claims 7-13, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the time of maximum concentration (T_{max}) of the compound ~~of Formula (I)~~ in the central nervous system (CNS) of the subject after administration is longer than that of non-isotopically enriched caffeine at an equivalent dose.

23. The beverage, food product, nutraceutical composition, or cosmetic composition of any one of claims 1-6 and 8-13, or the pharmaceutical composition of any one of claims 7-13, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein the total exposure (AUC) of the compound in the central nervous system (CNS) of the subject after administration is greater than that of non-isotopically enriched caffeine at an equivalent dose.

~~20~~24. A pharmaceutical composition of any one of claims 7-13 or a nutraceutical composition of any one of claims ~~1-11~~1-6 and 8-13; or ~~a compound of Formula (I)~~compound (**14**):



(**14**) ~~(I)~~,

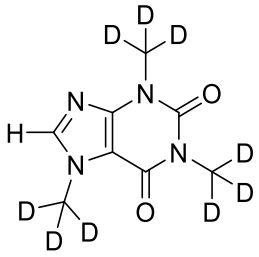
or a pharmaceutically or nutraceutically acceptable salt thereof;

~~wherein each Y is independently hydrogen or deuterium; and~~

~~at least one Y is deuterium;~~

for use in therapy.

25. A method of increasing energy levels, causing weight loss, increasing metabolic rate, reducing appetite, increasing energy expenditure, increasing urine output, or increasing sodium excretion, the method comprising administering to the subject a composition comprising of compound (**14**):



(**14**)

or a pharmaceutically or nutraceutically acceptable salt thereof.

26. The method of claim 25, wherein side effects are reduced relative to the administration of caffeine at an equivalent dose.

27. The method of claim 26, wherein the side effect is anxiety, insomnia, gastrointestinal issues, rhabdomyolysis, addiction, hypertension, rapid heart rate, atrial fibrillation, fatigue, irritability, nervousness, restlessness, nausea, or muscle tremors.