WHITE PAPER

d9-Caffeine

A Next-Generation Functional Caffeine with Preserved Pharmacodynamics and Enhanced Pharmacokinetic Performance

MOLECULAR FORMULA	$C_8HD_9N_4O_2$
PATENTS	US 10,582,716 · 10,765,130 · 11,547,127 · 11,666,073
SUPPORTING PEER-REVIEWED DATA	Parente RM, et al. *Food and Chemical Toxicology*. 2022;160:112774. Sherman MM, et al. *Regulatory Toxicology and Pharmacology*. 2022;133:105194.
PUBLISHED BY	**d9 Designs** · d9designs.com

Executive Summary

Caffeine is the most widely consumed bioactive stimulant molecule in the world, with well-characterized adenosine receptor antagonism resulting in its ergogenic and cognitive effects. With over a century of chemical familiarity, caffeine's pharmacokinetic profile is the result of extensive first-pass systemic metabolism through cytochrome P450 1A2 (CYP1A2) enzymes. This results in some noteworthy limitations in its use for performance, clinical, and consumer consumption applications. These include a short half-life, substantial inter-individual variability driven by CYP1A2 variability, and systemic exposure to paraxanthine, theobromine, and theophylline. These three pharmacologically active metabolites contribute to the typical side-effect profile of caffeine commonly described as jitters, sleep disruption, and "crash."

Deura9® is a deuterated form of caffeine (d9-caffeine) where the nine non-exchangeable hydrogens on the three methyl groups have been replaced with deuterium, a heavier rare but natural form of hydrogen. The subsequently formed carbon–deuterium bond is approximately six- to ten-fold more resistant to CYP-mediated cleavage than the carbon–hydrogen bond, a phenomenon known as the deuterium kinetic isotope effect (DKIE). This effect requires a greater amount of potential energy to break carbon-deuterium bonds than carbon-hydrogen bonds. The result is a molecule that binds to adenosine receptors like caffeine but is metabolized substantially more slowly, producing a fundamentally different pharmacokinetic profile.

Two peer-reviewed studies highlight the chemical and pharmacokinetic characteristics of Deura9. Parente et al. (2022) demonstrate functional equivalence at all four human adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, A_3), with IC_{50} potency values and rank-order potency comparable to caffeine. Sherman et al. (2022) report a randomized, double-blind, two-period crossover trial in eighteen healthy adults at 50 mg and 250 mg doses, with the following key findings:

- **Plasma half-life** is 17.8–18.2 hours for d9-caffeine vs. 4.2–5.4 hours for caffeine resulting in a 3.4× to 4.2× extension.
- **Plasma exposure (AUClast)** is 4.35 times greater at 50 mg and 4.82 times greater at 250 mg vs. an equimolar dose of caffeine.
- **Active metabolite AUC** is five- to ten-fold lower for paraxanthine, theobromine, and theophylline.
- **Inter-individual variability** is significantly reduced between normal metabolizers versus rapid metabolizers of caffeine
- **Dose-proportional pharmacokinetics** demonstrated a clean safety profile, with no clinically significant changes in vital signs, ECG parameters, or sleep patterns vs. caffeine.

Standard genotoxicity assays including bacterial reverse mutation (Ames) and *in vitro* mammalian cell micronucleus provided negative results, consistent with caffeine's established safety profile.

For sports medicine, clinical research, and functional nutrition applications, Deura9 introduces a novel ergogenic option. It preserves the complete pharmacological and physiologic mechanism of caffeine while exhibiting an extended, highly consistent pharmacokinetic profile characterized by a stabilized plasma concentration.

3.4–4.2×
EXTENDED PLASMA HALF-LIFE

4.35×
GREATER AUC AT 50 MG

4.82×
GREATER AUC AT 250 MG

5–10×
LOWER ACTIVE METABOLITE AUC

1. Introduction: The Pharmacokinetic Limitations of Caffeine

Caffeine (1,3,7-trimethylxanthine) exerts its principal pharmacological effects through competitive antagonism at adenosine receptors, displacing adenosine, primarily with the A_1 and A_{2A} subtypes. This mechanism contributes to its ergogenic effects on energy endurance, muscular performance, perceived exertion, and cognitive function. and accounts for caffeine's inclusion as a stimulant in the International Olympic Committee's monitoring program within the World Anti-Doping Agency (WADA).

The effects of caffeine as an ergogenic active ingredient are not due solely to its receptor pharmacology but also to its metabolism. Several of its pharmacokinetic features are particularly noteworthy:

1.1 Short plasma half-life

Caffeine is rapidly demethylated by CYP1A2 in the liver, producing paraxanthine (84%), theobromine (12%), and theophylline (4%) as the primary metabolites. The resulting plasma half-life of roughly four to six hours requires repeated dosing to maintain effective concentrations during prolonged training, competition, or shift-work settings, and tightly couples long term therapeutic effect to peak-and-trough fluctuation.

1.2 Blood level variability

CYP1A2 activity varies markedly across the population. Polymorphisms in the CYP1A2 gene (notably the -163C>A variant) produce “fast” and “slow” metabolizer phenotypes whose plasma caffeine concentrations after an identical dose can differ by 30–60% or more. Thus, the effects of caffeine vary from person to person due to differences in the rate of caffeine metabolism.

1.3 Pharmacologically active metabolites

Paraxanthine, theobromine, and theophylline are not inert metabolites. Each retains adenosine receptor activity, and theophylline also contributes to cardiovascular and sleep-related effects at the levels produced by a typical caffeine dose. The subjective profile commonly described as “jitters,” “crash,” and impaired sleep latency is best understood not due to caffeine itself, but as the action of caffeine's metabolite cascade superimposed on caffeine's primary effect.

> **The core question**
>
> *Can the pharmacodynamic mechanism of caffeine due to its CNS receptor effect be retained while the metabolic activity that drives its limitations is fundamentally reduced? Deuteration of caffeine's metabolic sites could be the answer to that question.*

2. The Deuterium Kinetic Isotope Effect

Deuterium (^{2}H, D) is a stable, non-radioactive heavier isotope of hydrogen with one additional neutron. The carbon–deuterium (C–D) bond is chemically and pharmacologically identical to the carbon–hydrogen (C–H) bond but is approximately six to ten times more resistant to enzymatic cleavage due to the greater amount of energy required to break the bond. This phenomenon, the deuterium kinetic isotope effect, or DKIE, is well-characterized in medicinal chemistry and has been validated in regulatory assessments including the FDA approval of deutetrabenazine (sold as Austedo and Austedo XR) in 2017, the first deuterated drug to reach the U.S. market.

DKIE is most pronounced when the C–H bond being broken is part of the rate-limiting step of metabolism. Caffeine's principal metabolic pathway is N-demethylation by CYP1A2, in which a methyl group is removed from each of the three xanthine nitrogen branches, is the rate-limiting step of N-demethylation involves cleavage of a C–H bond on the methyl carbon. By replacing the nine non-exchangeable methyl hydrogens of caffeine with deuterium, Deura9 directly targets each of those rate-limiting bonds.

Deura9 is not a caffeine analogue, salt, or co-crystal. It is caffeine with isotopic substitutions at the three metabolically targeted methyl groups. However, the adenosine receptor-binding portion of the molecules, which are the purine ring nitrogen and carbonyl groups, remain unchanged.

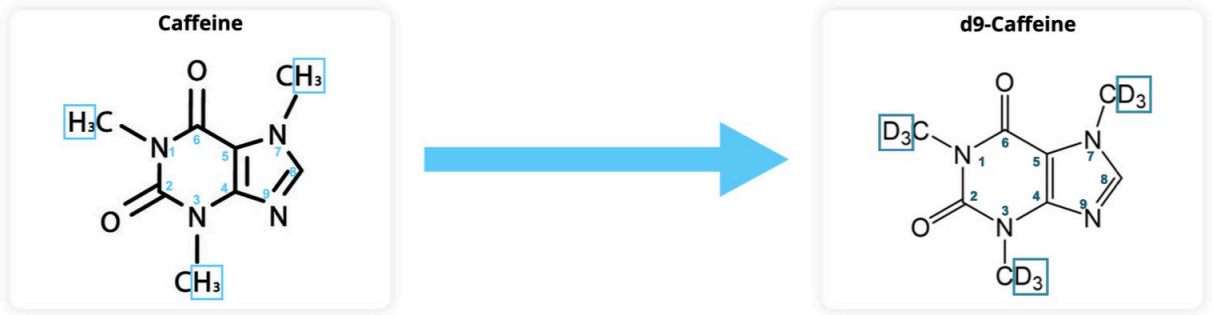
> **Why deuteration, and not analogue design?**
>
> *Analogues of caffeine that resist CYP1A2 metabolism by altering the methyl substituents (e.g., propylxanthines) inevitably also change receptor affinity, selectivity, or both. Deuteration is the rare structural intervention that decouples metabolism from pharmacodynamics: the receptor recognizes an unchanged molecule, and the enzyme targets a more resistant one.*

3. Deura9: Molecular and Regulatory Profile

Deura9 is synthesized through controlled exchange chemistry at the three methyl carbons of the xanthine backbone, yielding a deuterated molecule with isotopic enrichment of at least 99%. The single non-exchangeable hydrogen at the C-8 position of the purine ring is retained, preserving its receptor activity, and is consistent with the molecular formula $C_8HD_9N_4O_2$.

The GRAS recommended consumable dose is 45 mg per serving with a maximum recommended daily dose of 90 mg based upon its pharmacologic profile and relative AUC blood levels achieved over time. The pivotal pharmacokinetic study demonstrated that 1 mg of Deura9 resulted in an AUC over time equivalent to 4.3 mg of caffeine.

PROPERTY	VALUE
Chemical name	1,3,7-tri(methyl-d_3) xanthine (d9-caffeine)
Molecular formula	$C_8HD_9N_4O_2$
Molecular weight	~203.2 g/mol (vs. ~194.2 g/mol for caffeine)
Isotopic enrichment	≥99% deuterium at all nine methyl positions
Mechanism of action	Non-selective adenosine receptor antagonist (A_1, A_{2A}, A_{2B}, A_3)
Patents	US 10,582,716 · 10,765,130 · 11,547,127 · 11,666,073
Commercial dosing	45 mg suggested serving; 90 mg maximum per serving



4. Preserved Mechanism: Adenosine Receptor Pharmacodynamics

Reference: Parente RM, Tarka SM, Bruno R, et al. Pharmacological and toxicological evaluation of d9-caffeine. Food and Chemical Toxicology. 2022;160:112774.

Parente et al. addressed whether isotopic substitution alters the receptor activity of Deura9 through radioligand binding and functional assays at all four cloned human adenosine receptor subtypes.

4.1 Binding affinity and functional antagonism

Potency, measured as IC_{50} values, for d9-caffeine and caffeine were determined across the A_1, A_{2A}, A_{2B}, and A_3 receptors. The IC_{50} values for both molecules were essentially equivalent, and the rank-order potency was consistent with expected values where $A_{2A} > A_{2B} > A_1 > A_3$. Representative IC_{50} values reported for the A_{2A} receptor, the subtype most directly implicated in caffeine's ergogenic effects, were approximately 27.6 µM for caffeine and 30.9 µM for d9-caffeine, which is within typical assay-to-assay variability.

4.2 Functional implication

The mechanism of action by which caffeine produces its ergogenic, cognitive, and physiological effects by competitive antagonism at CNS adenosine receptors, is preserved in Deura9. From the perspective of the target receptor, both molecular entities are functionally indistinguishable. This biophysical equivalence is the prerequisite that allows the pharmacokinetic parameters to highlight its clinical differentiation. In this case, an optimized exposure profile is only advantageous if the downstream pharmacodynamic mechanisms remain intact.

RECEPTOR	CAFFEINE IC_{50}	D9-CAFFEINE IC_{50}	OUTCOME
A_1	Established µM range	Equivalent	**Matched**
A_{2A}	~27.6 µM	~30.9 µM	**Matched**
A_{2B}	Established µM range	Equivalent	**Matched**
A_3	Established µM range	Equivalent	**Matched**

Same mechanism, different metabolism

Deura9 preserves the pharmacodynamic profile of conventional caffeine as an adenosine receptor antagonist while utilizing deuteration to alter the pharmacokinetics responsible for its rapid hepatic clearance and downstream metabolite accumulation. This molecular modification forms the foundational premise of the compound.

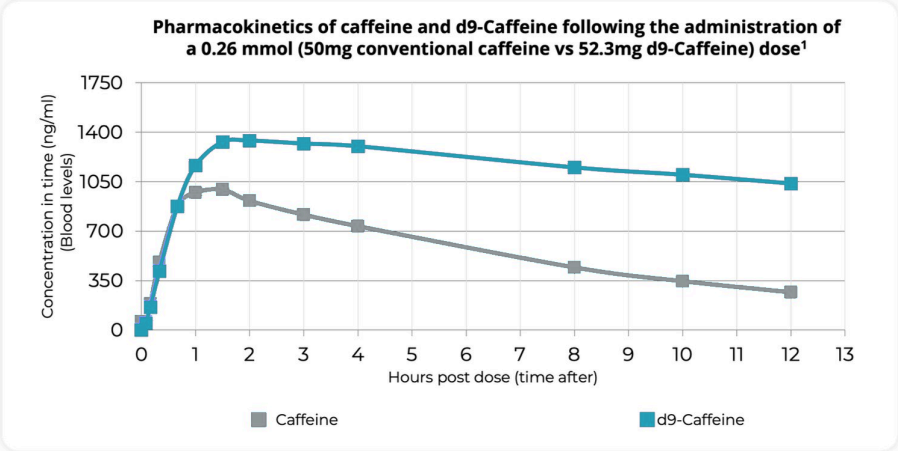
5. Enhanced Pharmacokinetics: Human Clinical Data

Reference: Sherman MM, Tarka SM, Bruno R, et al. Pharmacokinetics of d9-caffeine in healthy adults: a randomized, double-blind, two-period crossover study. Regulatory Toxicology and Pharmacology. 2022;133:105194.

The pivotal human pharmacokinetic study compared d9-caffeine and caffeine in a randomized, double-blind, two-period crossover design in eighteen healthy adults at two oral dose levels (50 mg and 250 mg). Plasma concentrations of the parent compound and the three major active metabolites were measured over a 72-hour window, and standard non-compartmental pharmacokinetic parameters were calculated for each subject.

5.1 Extended plasma half-life

Across both dose levels, the mean elimination half-life of d9-caffeine was 17.8–18.2 hours, compared with 4.2–5.4 hours for caffeine. This represents a 3.4× to 4.2× extension of plasma residence time. Mean residence time (MRT) followed the same pattern, with d9-caffeine producing 2.7× to 2.8× longer MRT values than caffeine across the dose range. The longer half-life is the direct result of the deuterium kinetic isotope effect operating at CYP1A2.



5.2 Increased plasma exposure (AUC)

Total plasma exposure, as measured by area under the concentration-time curve (AUClast), was substantially higher for d9-caffeine than for an equimolar dose of caffeine. At the 50 mg dose, d9-caffeine produced an AUClast 335% (4.35 times) higher than caffeine; at 250 mg, the difference was 382% (4.82 times) higher. Peak plasma concentration (Cmax) was modestly higher for d9-caffeine (approximately 29–43% higher than caffeine), indicating that the bulk of

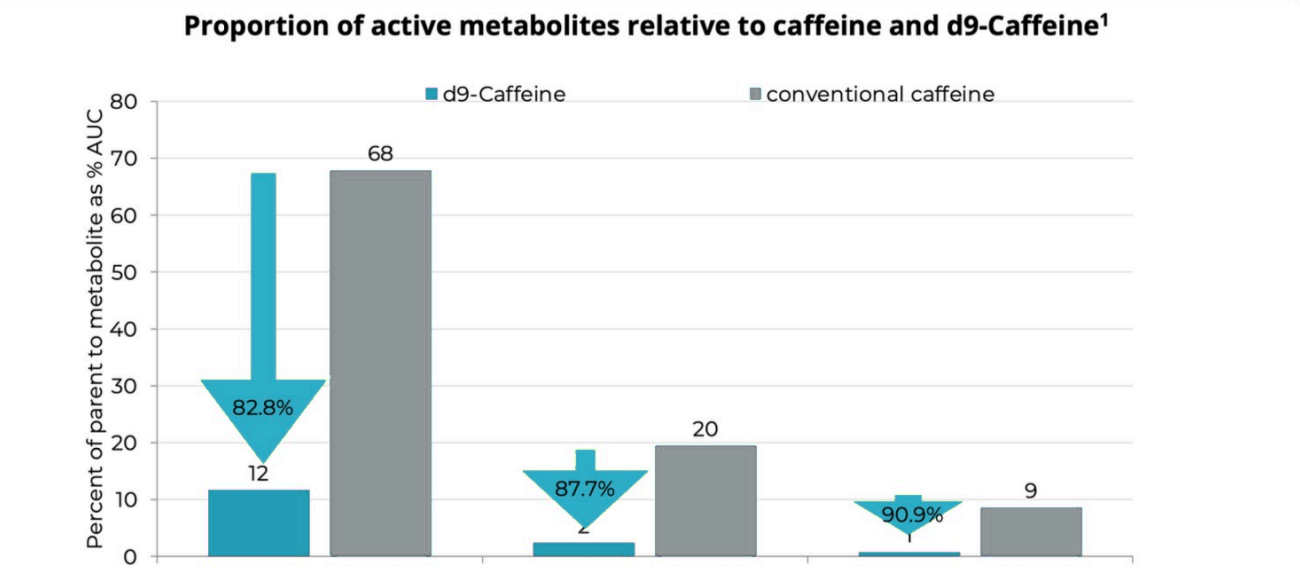
the AUC differential is driven by extended exposure rather than by a higher peak. The pharmacokinetic curve, in other words, is a flatter, longer curve rather than a higher, peaked curve.

PARAMETER	CAFFEINE	DEURA9	RATIO
Elimination half-life ($t_{½}$)	4.2–5.4 h	17.8–18.2 h	**3.4–4.2×**
Mean residence time (MRT)	Baseline	2.7–2.8× longer	**2.7–2.8×**
AUClast at 50 mg (vs. equimolar caffeine)	Baseline	+335%	**~4.4×**
AUClast at 250 mg	Baseline	+382%	**~4.8×**
Cmax	Baseline	+29–43%	**~1.3–1.4×**
Median Tmax	1.0–1.5 h	1.5–2.0 h	*Comparable*

5.3 Reduced active-metabolite burden

Plasma exposure to the three major active metabolites of caffeine (paraxanthine, theobromine, and theophylline) was substantially lower with d9-caffeine than with caffeine. AUC ratios for each metabolite were five- to ten-fold lower across the dose range, while the rank-order of metabolite concentrations (paraxanthine > theobromine > theophylline) was preserved. This reduction is the biochemical consequence of impeding CYP1A2-mediated demethylation where total systemic exposure to those metabolites is reduced accordingly.

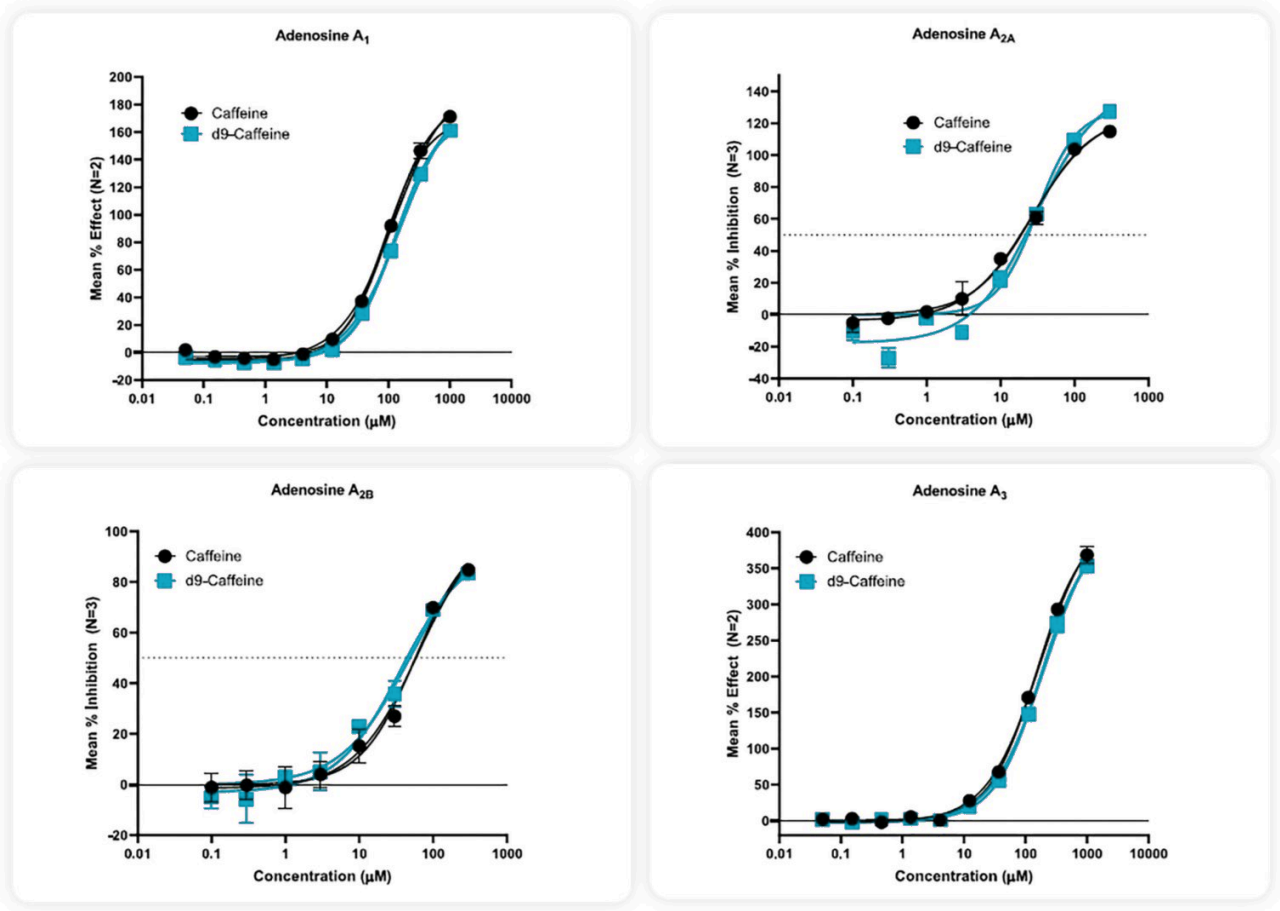
The clinical significance related to the active metabolites of caffeine, particularly theophylline, is the independently linked cardiovascular, gastrointestinal, and sleep-related side effects often attributed to caffeine itself.



5.4 Consistency across CYP1A2 metabolizer phenotypes

Subjects in the Sherman study were stratified by CYP1A2 metabolizer phenotype (normal vs. fast). For caffeine, plasma exposure varied between phenotype groups, consistent with published reports of CYP1A2-driven variability. For d9-caffeine, plasma levels were not impacted by metabolism. The practical implication is that it results in a more uniform exposure profile across the general population than caffeine at the same dose.

> A 45 mg or 90 mg dose of caffeine results in variable blood levels because individual metabolism depends heavily on CYP1A2. In contrast, a similar dose of Deura9 yields a more consistent exposure profile across the same population. For dose-response research, and consumer consumption recommendations, this represents a significant improvement in blood level predictability.



6. Safety and Tolerability

The safety profile supporting Deura9 is the result of studies performed with the standard criteria and tests applied to novel food ingredients and pharmaceutical entities of comparable structure.

6.1 Genotoxicity

Standard genotoxicity testing was negative across two complementary assays:

- **Ames bacterial reverse mutation assay** was negative for mutagenic activity across all tested strains, with and without metabolic activation.
- **In vitro mammalian cell micronucleus assay** was negative for clastogenic and aneugenic activity.

These results are consistent with the well-characterized non-genotoxic profile of caffeine and confirm that isotopic substitution at the methyl positions does not introduce genotoxic characteristics.

6.2 Clinical tolerability

In the human crossover study, both doses (50 mg and 250 mg) of d9-caffeine were well tolerated. Reported findings included:

- No clinically significant changes in heart rate, blood pressure, or ECG parameters.
- No significant difference in adverse event frequency or severity vs. caffeine at the same molar dose.
- No signal of disrupted sleep architecture or insomnia within the observation window.

Tolerability findings should be interpreted in the context of dose. At 250 mg, plasma concentrations of d9-caffeine substantially exceed those produced by typical caffeine consumption due to the AUC differences; at the GRAS recommended dose range of 45 mg per serving and 90 mg maximum recommended daily dose, exposure is well within the blood level range routinely tolerated in caffeine-naive and caffeine-experienced populations.

6.3 Pharmaceutical precedent for deuterated actives

Deuterated drugs are part of a regulatory-validated chemical class. Deutetrabenazine (Austedo®, approved 2017) and donafenib (approved 2021) established the principle that deuterium substitution to modify metabolism does not constitute a new pharmacological entity requiring *de novo* safety characterization beyond what is appropriate for the parent compound. Deura9 exists within this established framework, with safety supported by the existing toxicology and clinical literature for caffeine and human and *in vitro* data described above.

7. Applications in Sports Medicine and Performance Nutrition

. The extended half-life, increased plasma exposure, reduced metabolite burden, and reduced inter-individual variability associated with the pharmacokinetic profile of Deura9 creates real world opportunities where standard caffeine is poorly suited.

7.1 Endurance and long-duration competition

Standard caffeine dosing for endurance events typically requires re-dosing every 60 to 90 minutes to maintain plasma concentrations above the ergogenic threshold. A single Deura9 dose produces sustained plasma levels across the typical duration of marathon, ultra-endurance, multi-event tournament, or shift-work performance windows. This reduces the dosing needs and the peak-trough variability that compromises stable exposure over long durations.

7.2 CYP1A2-independent dosing protocols

Clinical and applied sports research protocols that rely on fixed-dose caffeine interventions are systematically confounded by CYP1A2 variability. The reduced variability of Deura9 plasma levels enables more uniform pharmacological exposure across clinical study participants and consumers, improving both the interpretability of research findings and the consistency of consumer experience.

7.3 Reduced metabolite-driven side effects

The five- to ten-fold reduction in active metabolite exposure provides a mechanistic basis for product positioning around reduced jitters, reduced gastrointestinal effects, and improved sleep latency at functionally equivalent receptor affinity. These claims are framed in terms of the measured metabolite reduction rather than subjective experience claims, which were not endpoints of the pivotal trial.

7.4 Cognitive performance and shift work

Sustained cognitive demand such as overnight shift work, military operations, long-haul travel requirements have historically relied on either repeated caffeine dosing or modafinil-class wakefulness drugs. Deura9 represents a practical option as a single dose with caffeine's similar mechanism of action, an exposure window measured in hours rather than minutes, and reduced metabolite-driven sleep disruption.

7.5 Formulation considerations

For formulators, Deura9 is dosed on a substantially lower mass weight when accounting for its duration of effect. The 45 mg suggested serving and 90 mg daily dose represent the practical GRAS commercial dose range; product formulations including beverages, capsules, gummies, and functional foods are compatible with the molecule's stability and solubility profile.

8. Summary: A New Class of Functional Caffeine

The pharmacological rationale for Deura9 is based on important structural insight applied with a focus on its pharmacokinetics while retaining its chemical and physiologic properties. Caffeine's value as a functional ingredient derives entirely from its adenosine receptor pharmacology, and its limitations are based on its metabolism. Deuteration of the three methyl groups as the metabolic target sites of the molecule produces a molecule that is pharmacodynamically indistinguishable from caffeine but pharmacokinetically distinct.

For the sports medicine, performance nutrition, and clinical research communities, Deura9 is neither a stimulant analogue nor a delivery technology applied to caffeine. Deura9 is a patented, deuterium-modified form of caffeine (d9-caffeine) that re-engineers the molecule's chemical bonds rather than using artificial time-release coatings. By leveraging the deuterium kinetic isotope effect to slow metabolic breakdown, it provides sustained, perceived crash-free ergogenics with drastically reduced exposure to downstream active metabolites.

Additional preclinical and clinical work is ongoing. d9 Designs welcome academic and clinical collaboration with research groups in exercise physiology, sleep science, neuropharmacology, and applied nutrition.

PROPERTY	DEURA9 VS. CAFFEINE
Adenosine receptor activity	**Matched at A_1, A_{2A}, A_{2B}, A_3**
Plasma half-life	**3.4–4.2× longer**
Plasma exposure (AUC)	**335–382% higher (equimolar)**
Active metabolite exposure	**5–10× lower across paraxanthine, theobromine, theophylline**
CYP1A2 phenotype variability	**Reduced from 32–62% to <18% (and <1% at 50 mg)**
Genotoxicity	**Negative (Ames; *in vitro* micronucleus)**
IP status	**US 10,582,716 · 10,765,130 · 11,547,127 · 11,666,073**

References

01 Parente RM, Tarka SM, Bruno R, et al. Pharmacological and toxicological evaluation of d9-caffeine. *Food and Chemical Toxicology.* 2022;160:112774.

02 Sherman MM, Tarka SM, Bruno R, et al. Pharmacokinetics of d9-caffeine in healthy adults: a randomized, double-blind, two-period crossover study. *Regulatory Toxicology and Pharmacology.* 2022;133:105194.

03 Pirmohamed M. Deuterium in drug discovery and development. *British Journal of Clinical Pharmacology.* 2020;86(8):1531–1532.

04 Schmidt C. First deuterated drug approved. *Nature Biotechnology.* 2017;35(6):493–494.

05 Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews.* 1999;51(1):83–133.

06 Nehlig A. Interindividual differences in caffeine metabolism and factors driving caffeine consumption. *Pharmacological Reviews.* 2018;70(2):384–411.

07 Guest NS, VanDusseldorp TA, Nelson MT, et al. International Society of Sports Nutrition position stand: caffeine and exercise performance. *Journal of the International Society of Sports Nutrition.* 2021;18(1):1.

08 United States Patent and Trademark Office. US Patent No. 11,299,114 B2. d9 Designs, assignee.

Published by d9 Designs · d9designs.com