A Toxicological Assessment of Methylliberine

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Abstract/Poster ID
3541/P337

Abstract

Methylliberine (CAS 51168-26-4) is a methoxiuric acid found at low levels in various *Coffea* plants (and likely other caffeine containing genera) as a metabolite of caffeine, theacrine, and liberine. No toxicological investigations on this compound were found in the literature. We studied the toxicological potential of a pure form of this compound (supplied by Compound Solutions, Inc.) according to internationally accepted guidelines in (1) a bacterial reverse mutation test, (2) an in vitro mammalian chromosomal aberration test, (3) an in vivo mammalian micronucleus test, and (4) a 14-day repeated-dose oral toxicity study in rats. The in vitro studies revealed no mutagenic or clastogenic activity of the test article both in the absence and presence of metabolic activation up to the maximum OECD recommended test concentrations. There was also no genotoxicity noted in the mammalian micronucleus study up to the highest dose tested of 700 mg/kg bw (given twice at a 24-hour interval). No mortality or effects that were considered toxicologically relevant were observed in Hsd.Han:WIST rats in the 14-day gavage study at doses of 55, 110, and 220 mg/kg bw/day, and the NOAEL was determined to be the highest dose level tested in both male and female rats.

Introduction

- IUPAC Name: 2-methoxy-1,7,9-trimethylpurine-6,8-dione (synonyms *O*(2),1,7,9-tetramethylurate; *O*(2),1,7,9-tetramethyluric acid).
- Molecular formula $C_9H_{12}N_4O_3$, molecular weight 224.22 g/mol.
- Methylliberine is structurally similar to methylxanthines such as caffeine and theobromine.
- The pharmacodynamic effects of methylliberine have not been studied but are thought to be similar to those of caffeine without the stimulant effect.
- Pharmacokinetically, methylliberine is hypothesized to have shorter t_{max} and half-life and greater C_{max} with respect to theacrine, although this also has not been studied.

Test Item, Dynamine®

- Dynamine® is a synthetic, commercially available methylliberine manufactured by Compound Solutions, Inc. (Carlsbad, CA).
- >98% pure (HPLC) and meets food grade specifications.
- Lot numbers 49-KY20171201 and 2017252667 were used in the genetic toxicity and 14-day oral toxicity studies, respectively.
- The vehicle/controls were DMSO and Dulbecco's Modified Eagle's medium for the bacterial reverse mutation and in vitro chromosomal aberration tests, respectively.
- 1% methylcellulose was used as the vehicle/control in the animal studies.

Bacterial Reverse Mutation Test

OECD Test Guideline 471 and GLP compliant.

Test System: *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA.*

Test Concentrations: 5000, 1600, 500, 160, 50, 16, and 5 μg/plate.

Positive Controls: 4-Nitro-1,2-phenylenediamine (NPD), sodium azide (SAZ), 9-aminoacridine (9AA), methyl methanesulfonate (MMS), 2-aminoanthracene (2AA). 2AA was the positive control with metabolic activation for all tester strains. Without metabolic active positive controls were: NPD (TA98), SAZ (TA100 & TA1535), 9AA (TA1537), and MMS (WP2 *uvrA).* DMSO was the vehicle/negative control for NPD, 9AA, and 2AA. Ultrapure water was the vehicle/negative control for SAZ and MMS.

Metabolic activation system: post mitochondrial supernatant (S9) prepared from livers of Phenobarbital/β-naphthoflavone-induced rats.

Initial (plate incorporation method) and **confirmatory** (pre-incubation method) tests were conducted.

- **Outcome**: Methylliberine did not cause base substitution or frameshift mutations in either experiment up to the highest concentration tested with or without metabolic activation in any of the five bacterium tester strains.
- **Conclusion**: Methylliberine is not mutagenic under the applied conditions up to the maximum recommended concentration for soluble non-cytotoxic substances.

Concentrations (μg/plate)	*Salmonella typhimurium* tester strains																*Escherichia coli* WP2uvrA			
	TA 98				TA 100				TA 1535				TA 1537							
	-S9		+S9		-S9		+S9		-S9		+S9		-S9		+S9		-S9		+S9	
Mean values of revertants per plate Mutation rate (MR)	Mean	MR	Mean	MR	Mean	MR	Mean	MR	Mean	MR	Mean	MR	Mean	MR	Mean	MR	Mean	MR	Mean	MR
Initial Mutation Test (Plate Incorporation Test)																				
Untreated Control	18.7	1.02	30.7	1.10	69.7	1.00	97.0	1.06	8.3	0.96	13.7	0.85	9.0	1.17	6.3	0.90	21.0	1.07	33.3	0.97
DMSO Control	18.3	1.00	28.0	1.00	70.0	1.00	91.3	1.00	8.7	1.00	16.0	1.00	7.7	1.00	7.0	1.00	19.7	1.00	34.3	1.00
5000	22.3	1.22	17.3	0.62	27.7	0.40	21.3	0.23	8.7	1.00	7.7	0.48	5.0	0.65	8.7	1.24	20.7	1.05	20.0	0.58
1600	23.7	1.29	15.7	0.56	61.7	0.88	58.0	0.64	9.3	1.08	10.0	0.63	7.7	1.00	8.0	1.14	22.0	1.12	29.3	0.85
500	19.3	1.05	28.0	1.00	70.0	1.00	80.0	0.88	13.7	1.58	14.3	0.90	7.3	0.96	8.3	1.19	17.3	0.88	34.0	0.99
160	18.7	1.02	23.7	0.85	77.3	1.10	97.3	1.07	10.0	1.15	15.3	0.96	6.3	0.83	7.0	1.00	21.0	1.07	25.0	0.73
50	20.0	1.09	21.7	0.77	63.0	0.90	88.7	0.97	10.3	1.19	14.0	0.88	7.3	0.96	8.0	1.14	18.7	0.95	24.0	0.70
16	19.7	1.07	27.7	0.99	63.0	0.90	84.3	0.92	7.3	0.85	14.3	0.90	6.3	0.83	10.3	1.48	21.0	1.07	28.7	0.83
5	18.0	0.98	24.0	0.86	63.0	0.90	83.3	0.91	12.0	1.38	14.3	0.90	6.3	0.83	8.7	1.24	18.0	0.92	28.7	0.83
Confirmatory Mutation Test (Pre-Incubation Test)																				
Untreated Control	16.7	1.39	22.7	1.33	64.7	1.05	96.7	1.30	10.7	1.07	9.0	0.77	8.7	1.18	8.0	1.09	29.7	1.09	35.3	0.89
DMSO Control	12.0	1.00	17.0	1.00	61.7	1.00	74.3	1.00	10.0	1.00	11.7	1.00	7.3	1.00	7.3	1.00	27.3	1.00	39.7	1.00
5000	16.0	1.33	17.0	1.00	26.3	0.43	24.7	0.33	8.7	0.87	7.7	0.66	10.7	1.45	8.7	1.18	31.7	1.16	34.0	0.86
1600	18.7	1.56	19.7	1.16	50.0	0.81	69.3	0.93	9.3	0.93	7.7	0.66	12.0	1.64	7.7	1.05	33.7	1.23	33.3	0.84
500	14.7	1.22	20.7	1.22	61.3	0.99	88.7	1.19	11.7	1.17	9.0	0.77	8.0	1.09	7.0	0.95	25.7	0.94	39.0	0.98
160	18.3	1.53	24.7	1.45	63.0	1.02	98.0	1.32	10.7	1.07	11.0	0.94	8.3	1.14	7.7	1.05	25.3	0.93	42.3	1.07
50	19.0	1.58	24.7	1.45	62.7	1.02	99.0	1.33	10.0	1.00	10.3	0.89	7.7	1.05	8.0	1.09	20.0	0.73	40.7	1.03
16	15.7	1.31	19.0	1.12	62.0	1.01	94.0	1.26	8.0	0.80	11.3	0.97	6.0	0.82	7.7	1.05	27.0	0.99	40.0	1.01
5	10.3	0.86	18.7	1.10	58.7	0.95	96.3	1.30	11.3	1.13	11.3	0.97	6.7	0.91	8.3	1.14	28.3	1.04	41.0	1.03

Groups (n =5†)	Sampling time (hours following final treatment)	Total number of PCEs analysed	MPCE (per 4000 PCE)		PCE/ PCE+NCE	
			mean	± SD	mean	± SD
Historical Negative Control	24	260000	5.05	1.00	—	—
Concurrent Negative Control	24	20000	6.20	1.30	0.53	0.02
175 mg/kg bw	24	20000	5.80	1.64	0.52	0.01
350 mg/kg bw	24	20000	6.20	1.30	0.50	0.02
700 mg/kg bw	24	20000	6.80*	1.30	0.49	0.01
Positive Control (60mg/kg bw)	24	20000	141.00**	5.96	0.39	0.05

†Historical Negative Control (n = 65)
*p < 0.05 to the historical negative control (value was inside in the 95% control limits (2.87–7.23) of the historical control data)
**p < 0.01 to the concurrent and historical negative control

In Vitro Mammalian Chromosomal Aberration Test

OECD Test Guideline 473 and GLP compliant.

Test System: V79 (male Chinese hamster lung) cells.

Test Concentrations: 250, 500, 1000, & 2000 μg/mL (short-term treatments without and with metabolic activation); 125, 250, & 500 μg/mL (long-term treatments without metabolic activation) based on preliminary cytotoxicity testing.

Positive Controls: Ethyl methanesulfonate without metabolic activation, cyclophosphamide monohydrate with metabolic activation.

Metabolic activation system: post mitochondrial supernatant (S9) prepared from livers of Phenobarbital/β-naphthoflavone-induced rats.

Two independent experiments were conducted at treatment/sampling intervals of 3/20 hours (Experiment A without and with S9-mix), 20/20 and 20/28 hours (Experiment B without S9-mix), and 3/28 hours (Experiment B with S9-mix) .

- **Outcome:** No abnormal metaphases or statistically significant increases in structural aberrations or dose-responses occurred with or without metabolic activation under the tested conditions up to the highest concentrations tested.
- **Conclusion:** Methylliberine is not clastogenic under the applied conditions.

Groups	S9-mix	Treatment time	Sampling time	Cytotoxicity	MEAN NUMBER OF ABERRANT CELLS /150 CELLS		% OF ABERRANT CELLS	MEAN NUMBER OF ABERRATIONS / 150 CELLS		MEAN ABERRATIONS						
										CHROMOSOME			CHROMATID			OTHERS
					gap+	gap-	gap-	gap+	gap-	gap	del	exchange	gap	del	exchange	
Experiment A																
Test Item																
250 μg/mL	–	3 h	20 h	5	7	4	2.333	7	4	0	0	0	4	4	0	-
500 μg/mL	–	3 h	20 h	16	7	4	2.667	7	4	2	1	1	1	2	1	-
1000 μg/mL	–	3 h	20 h	27	9	5	3.000	9	5	1	1	1	4	3	0	-
2000 μg/mL	–	3 h	20 h	32	8	3	2.000	8	3	3	0	1	3	2	0	-
Vehicle Control	–	3 h	20 h	0	8	4	2.667	8	4	1	0	2	3	2	0	-
Positive Control	–	3 h	20 h	50	39**	33**	22.000	57**	38**	7	8	6	12	13	12	-
Test Item																
250 μg/mL	+	3 h	20 h	6	8	5	3.000	9	6	2	1	2	2	1	3	-
500 μg/mL	+	3 h	20 h	17	10	4	2.667	10	4	3	1	1	4	2	1	-
1000 μg/mL	+	3 h	20 h	20	9	5	3.000	9	5	1	1	1	4	1	2	-
2000 μg/mL	+	3 h	20 h	32	8	4	2.667	8	4	1	1	1	4	3	0	-
Vehicle Control	+	3 h	20 h	0	8	6	3.667	9	6	1	1	3	3	2	1	-
Positive Control	+	3 h	20 h	52	44**	38**	25.333	88**	59**	10	8	7	19	11	34	-
Experiment B																
Test Item																
125 μg/mL	–	20 h	20 h	6	7	4	2.333	8	4	1	1	1	3	2	1	-
250 μg/mL	–	20 h	20 h	20	9	4	2.667	9	4	1	1	1	4	2	1	-
500 μg/mL	–	20 h	20 h	56	8	3	2.000	8	3	2	1	1	3	1	0	-
Vehicle Control	–	20 h	20 h	0	6	3	2.000	6	3	1	0	1	2	2	0	-
Positive Control	–	20 h	20 h	52	41**	34**	22.667	67**	46**	8	7	7	13	13	20	-
Test Item																
125 μg/mL	–	20 h	28 h	6	6	3	2.000	6	3	1	0	2	2	2	0	-
250 μg/mL	–	20 h	28 h	22	7	3	2.667	8	3	2	1	0	3	2	1	-
500 μg/mL	–	20 h	28 h	56	8	4	2.667	9	4	1	0	2	4	3	0	-
Vehicle Control	–	20 h	28 h	0	7	4	2.333	7	4	1	0	2	3	2	1	-
Positive Control	–	20 h	28 h	49	46**	41**	27.000	73**	48**	7	7	7	18	16	20	-
Test Item																
250 μg/mL	+	3 h	28 h	4	7	3	2.000	7	3	0	1	1	4	2	0	-
500 μg/mL	+	3 h	28 h	23	8	4	2.333	8	4	2	0	1	3	2	1	-
1000 μg/mL	+	3 h	28 h	26	8	3	2.000	8	3	2	0	1	4	2	1	-
2000 μg/mL	+	3 h	28 h	33	9	4	2.333	10	4	2	1	2	4	1	0	-
Vehicle Control	+	3 h	28 h	0	7	3	2.000	7	3	1	0	2	4	2	0	-
Positive Control	+	3 h	28 h	53	45**	42**	27.667	89**	62**	8	9	9	20	17	28	-

**p < 0.01

In Vivo Mammalian Micronucleus Test

OECD Test Guideline 474 and GLP compliant.

Animals: Male Crl:NMRI BR mice.

Dose Levels: 175, 350, and 700 mg/kg bw (two treatments at a 24-hour interval).

Positive Control: Cyclophosphamide (one treatment, 60 mg/kg bw IP).

Bone Marrow Sampling: Once, 24 hours following the final treatment.

- **Outcomes:**
  - In the preliminary toxicity study conducted in 2 mice of each sex at 500, 1000, and 2000 mg/kg bw, all mice in the 2000 mg/kg bw group died following the first treatment. Some dose-related signs of toxicity, persisting approximately 5 hours, were observed in the lower doses.
  - In the main study, no deaths occurred. No abnormal clinical signs were noted in the low dose group; moderately decreased activity was observed following dosing in the mid-dose group; decreased activity, narrow palpebra, hunchback posture, piloerection, and increased respiration rate of a heavy degree were observed in the high-dose group. Signs persisted 4 to 5 hours following treatments.
  - No biologically or statistically significant increases in micronucleated polychromatic erythrocytes were observed in bone marrow of treated mice compared to concurrent and historical negative controls up to the highest dose tested.
- **Conclusion:** Methylliberine does not induce in vivo chromosomal damage in the bone marrow of mice under the tested conditions.

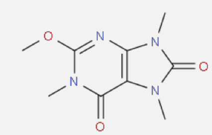
Fourteen-Day Dose-Range Finding Study

OECD Test Guideline 407 and GLP compliant.

Animals: Male and Female Hsd.Han:WIST rats.

Dose Levels: 55, 110, and 220 mg/kg bw/day.

Objectives: Obtain information on the toxic potential of methylliberine and for dose-selection for a 90-day repeated-dose study.

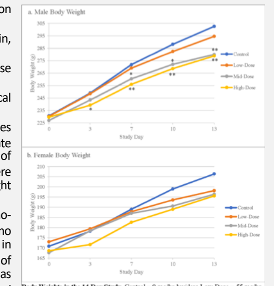


Methylliberine

- **Outcomes:**

Group	Treatment (mg/kg bw/d)							
	0		55		110		220	
	M	F	M	F	M	F	M	F
Animals (no.)	5	5	5	5	5	5	5	5
Deaths (no.)	0	0	0	0	0	0	0	0

- No clinical signs were observed. Behavior and physical condition were normal throughout.
- Toxicologically relevant effects on body weight, body weight gain, and food consumption were not observed.
- No eye alterations were observed in control or high-dose animals.
- No toxicologically relevant effects on hematology and clinical chemistry parameters were observed.
- Smaller than normal seminal vesicle (high-dose males), changes in weights of seminal vesicle with coagulating gland and prostate as a whole (mid- and high-dose males), and decreased amount of secretum in the seminal vesicles (high-dose males) were observed in the gross pathological exam, organ weight measurements, and histopathological exam, respectively.
- These changes were with minor degree and without any patho-histological lesion (degeneration, inflammation, fibrosis etc.); no related effects were observed with respect to spermatogenesis in the testicles of affected animals, and the histology of epididymites, prostate, and coagulating glands were normal as well. Therefore, the seminal vesicle effects were not considered to be toxicologically relevant.



Body Weights in the 14-Day Study. Control = 0 mg/kg bw/day; Low-Dose = 55 mg/kg bw/day; Mid-Dose = 110 mg/kg bw/day; High-Dose = 220 mg/kg bw/day; (a) Male body weights. (b) Female body weights. *p<0.05, **p<0.01.

- **Conclusions:**
  - The statistically significant reductions in body weight observed in the mid- and high-dose males were small (<10%) and, therefore, not considered toxicologically relevant.
  - The findings related to seminal vesicles could not be ruled out as test item-related nor could they be ruled out as as individual findings. Nonetheless, these findings were not considered adverse.
  - The no observed adverse effect level (NOAEL) was determined as 220 mg/kg bw/day.

Group (mg/kg bw/day)		WBC [x10⁹/L]	NEU [%]	LYM [%]	MONO [%]	EOS [%]	BASO [%]	RBC [x10¹²/L]	HGB [g/L]	HCT [L/L]	MCV [fL]	MCH [pg]	MCHC [g/L]	PLT [x10⁹/L]	RET [%]	PT [sec]	APTT [sec]
Male																	
Control	Mean	9.73	10.74	86.22	2.06	0.86	0.12	7.98	158.40	0.44	55.50	19.84	357.40	852.60	5.48	10.58	13.50
(n = 5)	SD	1.91	5.29	5.28	0.30	0.15	0.11	0.26	5.03	0.01	0.35	0.09	2.30	103.96	1.13	0.33	0.91
55	Mean	10.53	10.10	87.50	1.80	0.54	0.06	8.05	155.00	0.43	53.64	19.24	358.60	831.60	5.11	10.44	14.04
(n = 5)	SD	1.17	1.69	1.76	0.58	0.23	0.05	0.32	6.60	0.01	0.91	0.37	5.90	61.80	0.57	0.15	0.34
Statistical Significance						**					**	**					
110	Mean	11.72	10.98	86.46	2.06	0.42	0.08	7.84	160.80	0.45	56.98	20.54	360.00	804.40	5.61	10.54	14.54
(n = 5)	SD	1.76	2.00	2.10	0.33	0.11	0.04	0.11	3.27	0.01	0.77	0.19	3.54	114.07	1.26	0.40	0.62
Statistical Significance						**					**	**					*
220	Mean	11.06	10.92	86.50	2.18	0.34	0.06	8.32	165.00	0.45	54.30	19.84	365.20	838.60	5.92	10.68	15.64
(n = 5)	SD	1.36	3.16	3.96	0.93	0.11	0.05	0.29	5.96	0.01	0.67	0.34	7.19	60.57	1.06	0.23	0.79
Statistical Significance						**					*						**
Female																	
0 (Control)	Mean	7.01	12.12	84.92	1.80	1.16	0.00	7.90	151.20	0.41	52.42	19.16	365.60	835.80	4.70	10.42	14.74
(n = 5)	SD	1.60	5.14	5.42	0.53	0.81	0.00	0.23	2.17	0.00	1.17	0.47	2.30	93.38	0.92	0.37	0.52
55	Mean	7.00	11.92	85.56	1.60	0.90	0.02	7.91	151.40	0.42	52.42	19.16	364.80	814.40	4.22	10.42	15.42
(n = 5)	SD	1.41	2.24	2.20	0.70	0.31	0.04	0.30	9.13	0.02	2.00	0.76	1.92	55.73	0.42	0.36	1.02
110	Mean	7.58	11.94	85.50	2.02	0.54	0.00	7.71	148.00	0.41	52.76	19.22	364.00	831.00	4.60	10.14	15.22
(n = 5)	SD	0.99	3.42	3.49	0.48	0.27	0.00	0.38	4.85	0.01	2.01	0.65	2.24	57.24	0.88	0.36	0.81
220	Mean	9.33	12.18	85.26	2.00	0.56	0.00	7.87	151.00	0.41	52.64	19.18	364.60	885.60	5.67	9.98	15.76
(n = 5)	SD	1.30	1.50	2.23	0.74	0.32	0.00	0.24	6.86	0.02	0.80	0.37	4.10	172.74	0.57	0.31	0.86
Statistical Significance		*															

*p < 0.05; **p < 0.01

Group (mg/kg bw/day)		ALT [U/L]	AST [U/L]	ALP [U/L]	TBIL [μmol/L]	CREA [μmol/L]	UREA [mmol/L]	GLUC [mmol/L]	CHOL [mmol/L]	Pi [mmol/L]	Ca^{++} [mmol/L]	Na^{+} [mmol/L]	K^{+} [mmol/L]	Cl^{-} [mmol/L]	ALB [g/L]	TPROT [g/L]	A/G
Male																	
Control	Mean	66.22	111.82	239.40	1.10	18.24	8.56	6.89	1.70	2.74	2.87	141.00	4.60	103.24	32.96	61.68	1.16
(n = 10)	SD	10.20	11.52	33.32	0.28	1.48	1.46	0.43	0.13	0.14	0.04	0.71	0.19	0.30	0.47	1.59	0.09
55	Mean	69.54	110.72	264.00	0.65	16.62	7.21	7.19	1.88	2.65	2.82	140.40	4.53	103.12	32.20	58.76	1.20
(n = 5)	SD	5.83	17.56	112.52	0.22	0.56	0.75	0.45	0.31	0.08	0.04	0.89	0.29	0.51	0.44	0.87	0.07
Statistical Significance					*											*	
110	Mean	72.30	118.98	235.60	1.13	17.04	7.51	6.86	1.89	3.01	2.86	140.80	4.51	103.44	32.78	60.32	1.20
(n = 5)	SD	13.09	20.97	62.98	0.50	0.80	0.50	0.57	0.28	0.25	0.09	0.84	0.18	0.89	0.65	2.17	0.07
Statistical Significance										*							
220	Mean	93.56	115.44	218.40	1.11	18.84	9.08	7.07	2.24	2.57	2.88	141.20	4.42	103.82	32.44	59.10	1.20
(n = 5)	SD	8.28	5.01	66.99	0.15	2.18	1.13	0.50	0.26	0.17	0.06	0.84	0.25	0.71	0.51	2.06	0.07
Statistical Significance		**							**							*	
Female																	
0 (Control)	Mean	54.54	101.12	120.40	0.74	20.64	8.65	6.64	1.78	1.79	2.72	141.20	4.35	105.00	34.06	60.06	1.30
(n = 5)	SD	8.89	10.20	21.65	0.20	2.25	0.67	0.35	0.34	0.17	0.08	1.30	0.26	0.97	0.54	0.80	0.00
55	Mean	54.06	104.34	119.20	0.89	19.86	7.74	7.05	1.69	2.06	2.67	140.40	4.14	104.66	32.82	57.82	1.32
(n = 5)	SD	5.69	14.80	21.51	0.30	2.19	0.79	0.43	0.39	0.20	0.07	1.52	0.13	1.69	0.89	1.88	0.04
Statistical Significance										*					*		
110	Mean	71.36	117.28	120.80	1.00	19.04	7.90	7.00	2.53	1.93	2.57	139.60	4.36	104.28	32.16	56.08	1.32
(n = 5)	SD	8.18	8.48	50.84	0.16	1.62	1.58	0.41	0.26	0.21	0.07	1.67	0.35	1.30	0.66	2.49	0.08
Statistical Significance		**	*						*		**				**	**	
220	Mean	79.76	101.42	106.60	1.19	21.58	8.54	6.11	2.63	2.15	2.66	138.80	4.18	103.22	32.96	59.24	1.26
(n = 5)	SD	11.28	6.83	28.12	0.26	3.74	0.52	0.84	0.73	0.15	0.01	1.64	0.17	1.36	1.26	1.90	0.11
Statistical Significance		**			*				*	*							

*p < 0.05; **p < 0.01

Comments and Conclusions:

- Methylliberine lacks mutagenic potential.
- The findings of the 14-day study were used to determine doses for an OECD 408 90-day study, which is underway. Preliminary results have not indicated the presence to toxic effects or target organs.