Data Evaluation Report on the Acute Inhalation Toxicity of Iodomethane on Avian Species *Colinus virginianus*

PMRA Submission Number EPA MRID Number 45593717

Data Requirement:

PMRA DATA CODE:
EPA DP Barcode: D280800
OECD Data Point:
EPA MRID: 45593717
EPA Guideline: ~~71-1~~ acute inhalation

Test material: TM-425 **Purity:** 99.7%
Common name: Iodomethane
Chemical name: IUPAC: Iodomethane
CAS name: Not reported
CAS No.: 74-88-4
Synonyms: Not reported

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Date:

Reference/Submission No.:

Company Code:
Active Code:
EPA PC Code: 000011

Date Evaluation Completed:

CITATION: Kiplinger, G.R. 2002. Acute Inhalation Toxicity Study of Iodomethane in Bobwhite Quail. Unpublished study performed by WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No. WIL-418005. Study submitted by Arvesta Corporation, San Francisco, CA. Study initiated August 20, 2001 and completed January 23, 2002.

EXECUTIVE SUMMARY:

The acute inhalation toxicity of TM-425 (iodomethane) to 22- to 24-week-old Northern bobwhite quail (*Colinus virginianus*) was assessed over 14 days. Groups of five birds per sex were exposed by whole-body inhalation to TM-425 at measured concentrations of 0 (negative control), 344, 377, 392, 415, and 509 ppm for 4 hours. These concentrations are equivalent to 0, 1.94, 2.13, 2.22, 2.35, and 2.88 mg/L, respectively. Nominal concentrations were 441, 460, 490, 483, 552 ppm. The LC_{50} for the combined sexes was 395 ppm (2.23 mg/L), categorizing TM-425 as moderately toxic to bobwhite quail on an acute inhalation basis. The LOEC of TM-425, based on clinical signs of toxicity and body weight change, was 344 ppm (1.94 mg/L). Because treatment-related effects were observed at the lowest concentration tested, the NOEC was <344 ppm (<1.94 mg/L).

Mortality occurred in 0%, 0%, 20%, 60%, 70%, and 100% of birds exposed to 0, 344, 377, 392, 415, and 509 ppm TM-425, respectively, within 5 days of administration. Clinical effects were observed in all treatment groups upon chamber removal and included ataxia, gasping, rales, hypoactivity, prostration, clear ocular discharge, convulsions, and/or wet red material around beak. Effects completely subsided by Days 2, 4, 3, and 6 from surviving birds in the 344 ppm, 377, 392, and 415 ppm groups, respectively. Mean reductions in the body weights and body weight change of surviving animals were observed at all test levels between 0 and 14 days. Gross necropsy of the decedent birds revealed dark red discoloration of the lungs in one female each from the 392 and 509 ppm groups; necropsy of the birds sacrificed after 14 days revealed dark red discoloration of the lungs and a firm right lung lobe in one male from the 415 ppm group; no other treatment-related findings were observed.

As an inhalation study, this test is not a Subdivision E Guideline study. However, it appears to be scientifically sound, and is thus classified as Supplemental. The information that it provides is useful for risk assessment purposes.

Results Synopsis

Test Organism Size/Age : Approximately 22-24 weeks, 185-227 g (combined sexes)

LC_{50} (combined sexes): 395 ppm (2.23 mg/L) 95% C.I.: 372-414 ppm (2.10-2.34 mg/L)
NOEC: <344 ppm (<1.94 mg/L) Probit Slope: N/A
LOEC: 344 ppm (1.94 mg/L)
Endpoint(s) Affected: Mortality, clinical effects, body weight, and (to a lesser degree) lung abnormalities

I. MATERIALS AND METHODS REPORTED

GUIDELINE FOLLOWED: Although this study did not employ a conventional method of dose administration, the protocol generally followed procedures of the U.S. EPA Pesticide Assessment Guidelines, Subdivision E, Hazard Evaluation: Avian and Mammalian Testing, Section §71-1 (p. 8). Deviations from §71-1 are:

1) The route of exposure was whole-body inhalation, whereas the route of oral exposure for guideline §71-1 is gavage or gelatin capsule.

2) Quail were acclimated to laboratory conditions for a minimum of 7 days prior to test initiation. EPA requires that birds are maintained for at least 15 days.

3) The health of the quail during acclimation, including pre-test mortality, was not described.

4) The size of the cages used to house the quail was not specified.

5) The experimental photoperiod was 8 hours light/16 hours dark, whereas EPA recommends a 10-hour light/14-hour dark photo-period.

The deviation from the recommended method of oral exposure affected the acceptability, but not the validity of the study.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and No Data Confidentiality statements were provided. This study was conducted in accordance with both EPA and OECD Principles of GLP.

A. MATERIALS:

1. Test Material TM-425

Description: Deep yellow, translucent liquid

Lot No./Batch No.: 007403 Drum 2/02

Purity: 99.7%

Stability of Compound Under Test Conditions: Verified by analytical determination (via gas chromatography) of active ingredient during the 4-hour exposure period.

OECD requirements were not reported.

OECD requires water solubility, stability in water and light, pK_a, P_{ow}, and vapor pressure of the test compound.

Storage conditions of test chemicals: Amber glass bottles at ambient temperature.

2. Test organism:

Species: Bobwhite quail (*Colinus virginianus*)

Age at study initiation: Approximately 22-24 weeks old

Weight at study initiation: Males: 185-224 g; Females: 188-227 g

Source: Morgans Quail Farm, Warren, OH.

B. STUDY DESIGN:

1. Experimental Conditions

a) Range-finding Study: None reported.

b) Definitive Study:

Table 1. Experimental Parameters.

Parameter	Reported Details	Remarks *Criteria*
Acclimation period:	≥7 days	The acclimation period was shorter than recommended.
Conditions (same as test or not):	Same as test	
Feeding:	Purified (reverse osmosis-treated) municipal water and Harlan Teklad Duck and Quail Diet 7063 were provided *ad libitum*.	*EPA recommends that birds be pre-conditioned to the test facilities for at least 15 days.*
Health (any mortality observed):	Pre-test health/mortality was not described.	*OECD recommends that birds be pre-conditioned to the test facilities for at least 7 days.*

Parameter	Reported Details	Remarks *Criteria*
Pen size and construction materials	Suspended wire mesh cages; size not specified.	*EPA requires: pens must conform to good husbandry practices and should not create crowding stress.* *OECD lists no criteria for pen construction other than stating that pens should be suitable for the captive rearing of that species.*
Test duration	There was a 14-day observation period following exposure.	*EPA requires a day for dosing and at least 14 days observation.*
Dose preparation	Test atmospheres were generated by drawing compressed air through a gas washing bottle filled with the test chemical (p. 12 and Figure 1, p. 27); the resulting vapor was carried to the top of the exposure chamber with the appropriate flow of chamber dilution air.	
Method of confirmation of dose	The nominal test atmosphere concentration was calculated at the end of each exposure period by dividing the total amount of test material delivered to the chamber by the total air volume passing through the chamber during the exposure time. Actual concentrations were measured via gas chromatography at least every 30 minutes (8 to 13 times per exposure) during each exposure period. Samples were collected manually using a sampling valve and sample loop.	

Parameter	Reported Details	Remarks *Criteria*
Mode of dose administration	4-Hour, whole-body inhalation. Birds were exposed in one of two 1000 L glass and stainless steel whole-body exposure chambers (Hazleton-type). One chamber was used for the control group and the other for the TM-425-exposed groups.	Food and water were withheld during exposure. *Gavage or gelatin capsule.*
Dose levels nominal: measured:	0 (control), 350, 380, 400, 425, and 500 ppm; equivalent to 1.98, 2.15, 2.26, 2.40, and 2.83 mg/L. 0 (control), 344, 377, 392, 415, and 509 ppm, equivalent to 0, 1.94, 2.13, 2.22, 2.35, and 2.88 mg/L, respectively.	For all exposures, the total airflow through the chamber was maintained at 205-227 L/min [reviewer-calculated from total air volume (p. 16) assuming a 240-min exposure period]. This is equivalent to 12-13 chamber turnovers/hour (reviewer-calculated). The time required for 99% equilibration was 21-22 minutes (p. 17). Birds were exposed on days 1, 4, 7, 8, 9, and 14 from the experimental start date (September 25, 2001) to the 344, 509, 415, 0, 377, and 392 ppm groups, respectively. *EPA requires a minimum of 5 treatment levels unless LD_{50} is demonstrated to be greater than 2000 mg ai/kg*
Solvent/vehicle, if used type: amount/bw:	N/A	*EPA recommends that the test material be administered without a vehicle if possible. Maximum vehicle should not exceed 0.1 to 1.0% of body weight.*

Parameter	Reported Details	Remarks *Criteria*
Particle sizing	The mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and percentages of particles ≤10 µm were not calculated.	
Number of birds per groups/treatment for negative control: for solvent/vehicle control: for treated:	10 N/A 10 per test level	During exposure, birds were group housed (five per sex) and maintained in 1000 L glass and stainless steel exposure chambers (p. 12). *EPA recommends 10 birds per treatment group and 10 birds for each control and vehicle group.*
No. of feed withholding days before dosing	Food and water were provided to birds *ad libitum* during acclimation and were withheld during exposure.	*EPA recommends that food should be withheld for at least 15 hours prior to dosing.*
Photo-period:	8-hours light/16-hours dark	*EPA recommends that a 10 hr light/14 hr dark photo-period.*
Test conditions during exposure Temperature: Relative humidity: Oxygen level:	21-23˚C 37-50% Not reported, but it was measured during method development with a Mine Safety Appliances Remote Sampling Sensor (p. 12).	Temperature and humidity was determined eight times during each exposure period. The protocol specified that oxygen levels should be maintained at ≥19% (p. 180).
Reference chemical, if used name: concentrations tested:	None used	

2. Observations:

Table 2: Observations.

Parameter	Reported Details	Remarks/Criteria
Parameters measured		
Parameters measured (mortality/individual body weight at test initiation and termination/ mean feed consumption/ others)	-Mortality -Clinical signs of toxicity -Mean feed consumption (g/bird/day) -Individual body weights	*EPA recommends:* *Body weight measured at test initiation, on Day 14 and at end of the test if the test is extended beyond 14 days.* *Calculation of mortality. Mortality must NOT be more than 10% in controls.* *Feed consumption may be measured as average daily food consumption.*
Indicate if the test material was regurgitated	N/A	*Regurgitation is an indication that the does was rejected. The test may have to be repeated if the problem persists.*
Groups on which necropsies were performed	All decedent and surviving birds were subject to a gross pathological examination.	*EPA recommends that gross necropsies be performed with inspections of the GI tract, liver, kidneys, heart, and spleen.*
Observation intervals	Mortality: Midway through exposure, upon chamber removal, and twice daily thereafter Signs of Toxicity: Midway through exposure, upon chamber removal, and once daily thereafter Feed consumption: Daily Body Weight: Days 0, 7, and 14	
Were raw data included?	Yes, for body weight, body weight change, and mortality. Daily means for each treatment and sex were provided for food consumption.	

II. REPORTED RESULTS AND DISCUSSION:

A. MORTALITY:

Percent mortality increased with increasing concentrations of TM-425 and was 0%, 0%, 20%, 60%, 70%, and 100% in the control, 344, 377, 392, 415, and 509 ppm treatment groups, respectively. No significant gender differences were observed (p. 18).

Table 3: Effect of TM-425 on mortality of *Colinus virginianus*.

Treatment, ppm (mg/L)		No. of birds	Cumulative mortality					
			Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Negative control		10	0	0	0	0	0	0
344 (1.94)		10	0	0	0	0	0	0
377 (2.13)		10	1	2	2	2	2	2
392 (2.22)		10	0	3	4	5	5	6
415 (2.35)		10	4	7	7	7	7	7
509 (2.88)		10	10	10	10	10	10	10
NOEC		344 ppm (1.94 mg/L)						
LC_{50}		Combined sexes: 395 ppm (2.23 mg/L)						
Reference chemical	mortality	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	LD_{50}	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NOAEL	N/A	N/A	N/A	N/A	N/A	N/A	N/A

B. SUB-LETHAL TOXICITY ENDPOINTS:

During the exposure period, prostrate position was observed in 10/10 birds from the 509 ppm group and in 1/10 birds from the 415 ppm group; gasping was noted in 10/10 birds from the 415 ppm group, in 1/10 birds from the 392 ppm group, and in 9/10 birds from the 377 ppm group; and ataxia was observed in 2/10 birds from the 392 ppm group and in 1/10 birds from the 377 ppm group (Table 3A, pp. 41-45). Vocalization was also noted for 1/10 control birds during exposure. No effects were observed during exposure in quail exposed at 344 ppm. Upon chamber removal, signs of toxicity were observed in surviving birds from all exposure groups, and are summarized in Table 4. Effects completely subsided by Days 2, 4, 3, and 6 from surviving birds in the 344 ppm, 377, 392, and 415 ppm groups, respectively.

Table 4. Sub-lethal effects immediately following exposure of TM-425 on *Colinus virginianus*.

Treatment, ppm (mg/L)	Effect	Male	Female	Combined
Negative control	N/A	None	None	N/A
344 (1.94)	Ataxia Gasping Rales	1/5 3/5 2/5	0/5 3/5 3/5	1/10 6/10 5/10
377 (2.13)	Ataxia Gasping Hypoactivity Prostration Clear ocular discharge	1/5 5/5 4/5 1/5 0/5	3/5 5/5 2/5 1/5 1/5	4/10 10/10 6/10 2/10 1/10
392 (2.22)	Ataxia Gasping Hypoactivity	4/5 5/5 4/5	3/5 3/5 5/5	7/10 8/10 9/10
415 (2.35)	Ataxia Gasping Hypoactivity Prostration	3/5 5/5 4/5 1/5	4/5 5/5 4/5 2/5	7/10 10/10 8/10 3/10
509 (2.88)	Ataxia Convulsions Gasping Prostration Wet Red Material Around Beak	N/A[1] N/A N/A N/A N/A	2/4 1/4 4/4 4/4 1/4	2/4 1/4 4/4 4/4 1/4
NOAEC (sublethal)	<344 ppm (<1.94 mg/L)			
LOAEC (sublethal)	344 ppm (1.94 mg/L)			

[1] All males died during the exposure period.

Between 0 and 7 days, mean reductions in the body weights and body weight change of surviving animals were observed at all test levels, and were statistically significant when compared to controls for males at the 344, 377, and 415 ppm levels ($p<0.01$), and for females at the 344 and 377 ppm levels ($p<0.05$ or $p<0.01$; Table 5 below). All surviving birds, with the exception of one male from the 377 ppm group, gained weight between 7 and 14 days. Mean body weight gains were significantly higher ($p<0.01$) than controls in males from the 344 ppm group and in females from the 344 and 377 ppm groups. Regardless, only 4/10, 0/8, 2/4, and 0/3 surviving birds in the 344, 377, 392, and 415 ppm groups were reported to meet or exceed their initial body weight by the end of the study (p. 20).

Table 5: Body weight effects of TM-425 on *Colinus virginianus*.

Body Weight, g[1]						
Treatment, ppm (mg/L)	**Males**			**Females**		
	Day 0	**Day 7**	**Day 14**	**Day 0**	**Day 7**	**Day 14**
Negative control	202	205 (3)	206 (2)	207	207 (1)	211 (3)
344 (1.94)	199	185 (-14)**	197 (12)**	199	181** (-18)**	197 (15)**
377 (2.13)	207	198 (-14)**	202 (4)	205	185* (-20)**	197 (12)**
392 (2.22)	205	201 (-13)	209 (9)	208	186 (-14)	196 (10)
415 (2.35)	200	185 (-19)**	193 (8)	199	N/A	N/A
509 (2.88)	198	N/A	N/A	207	N/A	N/A
NOAEC (sublethal)	<344 ppm (<1.94 mg/L)			<344 ppm (<1.94 mg/L)		
LOAEC (sublethal)	344 ppm (1.94 mg/L)			344 ppm (1.94 mg/L)		

[1] Body weight changes are provided in parentheses.
* significantly different ($p < 0.05$)
** significantly different ($p < 0.01$)

No treatment-related effects on food consumption (calculated daily) were observed (Table 6, pp. 50-55). The changes noted were reportedly due to spillage, animal dusting, fecal deposition, etc., and were not considered by the study authors to be the result of exposure (p. 21).

Gross necropsy of the 25 decedent birds revealed dark red discoloration of the lungs in one female each from the 392 and 509 ppm groups; no other treatment-related findings were observed (Table 7, p. 56). Necropsy of the 35 birds sacrificed after 14 days revealed dark red discoloration of the lungs and a firm right lung lobe in one male from the 415 ppm group; no other treatment-related findings were observed (Table 8, p. 57).

C. REPORTED STATISTICS:

The acute inhalation LC_{50} value for combined sexes was calculated using the Litchfield and Wilcoxon method of analysis. Body weight and body weight gain data from each toxicant level were compared to control data using one-way analyses (ANOVA) followed by Dunnett's test. Analyses were conducted at 1 and 5% levels. Feed consumption data were not analyzed statistically.

D. VERIFICATION OF STATISTICAL RESULTS:

The NOEC for mortality and food consumption were verified visually, while the LC_{50} and 95% confidence

intervals were estimated using the moving average angle method via Toxanal software. Data for body weight change (day 0-14) satisfied the assumptions of normality and homogeneity of variances, so they were analyzed using ANOVA, followed by Bonferroni's t-test to determine the NOEC via TOXSTAT software.

Results Synopsis

LC_{50} (combined sexes): 395 ppm (2.23 mg/L) 95% C.I.: 372-414 ppm (2.10-2.34 mg/L)
NOEC: <344 ppm (<1.94 mg/L);body weight change Probit Slope: N/A
LOEC: 344 ppm (1.94 mg/L)
Endpoint(s) Affected: Mortality, clinical effects, body weight, and (to a lesser degree) lung abnormalities

E. STUDY DEFICIENCIES:

Being an inhalation study, this study is not a Subdivision E Guideline study. However, since this study appears to be scientifically sound, it is thus classified as Supplemental; it provides useful information for risk assessment purposes. Other deviations were considered to be minor, as the study generally adhered to the US EPA guidelines for an acute oral avian study.

F. REVIEWER'S COMMENTS:

The reviewer's conclusions were identical to the study author's. The LD_{50} was determined to be 395 ppm, which categorizes TM-425 (Iodomethane) as moderately toxic to bobwhite quail on an acute inhalation toxicity basis. The NOEC was <344 ppm, based on reductions in body weight change and clinical signs of toxicity. Food consumption was not adversely affected by treatment with TM-425.

In addition to Subdivision E, Series §71-1 guidance, the reviewer also incorporated applicable methodology guidance from Subdivision F, Hazard Evaluation: Inhalation Toxicity Testing, Series §81-3 (pertaining to human toxicology). In consideration of this guidance, the following deviations were observed:

- The mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and percentages of particles ≤ 10 µm were not calculated.
- It was not reported if oxygen levels were maintained at $\geq 19\%$.
- It was not specified where samples used for analytical determination were collected from within the test chambers. Due to potentially high variability within exposure chambers, samples should be collected from the breathing zone of the animals.

The LC_{50} was reportedly estimated by the study author using the method of Litchfield and Wilcoxon; however, its 95% confidence interval was not provided.

A slight discrepancy was observed in the study, which did not impact the study conclusions. It was noted that four birds from the 415 ppm group died during the 4-hour exposure period (p. 18). However, these mortalities were not listed under clinical signs immediately following chamber removal (p. 19). Furthermore, clinical signs noted during exposure did not include mortality as a finding in the 415 ppm group, while it was mentioned under clinical signs for the 509 ppm group (Table 3A, pp. 41-45).

Because data provided to EPA to fulfill the Subdivision F, Series §81-3 data requirement are presented in terms

of mg/L, both ppm and mg/L are presented in this DER for ease of cross-comparison. The conversion equation is presented on p. 17 of the study.

A Core acute oral toxicity study was submitted (MRID 45593716) that exposed bobwhite quail to Iodomethane via an EPA-accepted method of dose administration (gavage) and showed that it was moderately toxic on an acute oral basis (LD_{50} = 57 mg/kg).

G. CONCLUSIONS:

This toxicity study is scientifically sound, but it does not fulfill the guideline requirements for an acute oral toxicity study (US EPA, Subdivision E, FIFRA §71-1) because the method used to administer the test chemical (inhalation) was not a guideline-specified route of exposure. This study is classified as Supplemental and it provides useful information for risk assessment purposes regarding the acute toxicity of TM-425 (iodomethane) to Northern bobwhite quail via 4-hour (whole-body) inhalation exposure. The LD_{50} was estimated to be 395 ppm, which categorizes TM-425 as moderately toxic to bobwhite quail on an acute oral inhalation basis.

LC_{50} (combined sexes): 395 ppm (2.23 mg/L) 95% C.I.: 372-414 ppm (2.10-2.34 mg/L)
NOEC: <344 ppm (<1.94 mg/L);body weight change Probit Slope: N/A
LOEC: 344 ppm (1.94 mg/L)
Endpoint(s) Affected: Mortality, clinical effects, body weight, and (to a lesser degree) lung abnormalities

III. REFERENCES:

Dunnett, C.W. 1964. New tables for multiple comparisons with a control. Biometrics, 20: 482-491.

Litchfield, J.T. and F. Wilcoxon. 1949. A Simplified Method for Evaluating Dose-Effect Experiments, *Jour. Pharmacol. Exp. Ther.* 96: 99-113.

Snedecor, G.W. and W.G. Cochran. 1980. One-way Classifications; Analysis of Variance, *Statistical Methods*, 7th Edition. The Iowa Sate University Press, Ames, IA. pp. 215-237.

APPENDIX I. OUTPUT OF REVIEWER'S STATISTICAL VERIFICATION:

body weight change
File: 3717bwc Transform: NO TRANSFORMATION

ANOVA TABLE

SOURCE	DF	SS	MS	F
Between	4	971.701	242.925	10.250
Within (Error)	30	711.042	23.701	
Total	34	1682.743		

Critical F value = 2.69 (0.05,4,30)
Since F > Critical F REJECT Ho:All groups equal

body weight change
File: 3717bwc Transform: NO TRANSFORMATION

BONFERRONI T-TEST - TABLE 1 OF 2 Ho:Control<Treatment

GROUP	IDENTIFICATION	TRANSFORMED MEAN	MEAN CALCULATED IN ORIGINAL UNITS	T STAT	SIG
1	0	4.100	4.100		
2	344	-1.200	-1.200	2.434	*
3	377	-8.375	-8.375	5.402	*
4	392	-4.000	-4.000	2.812	*
5	415	-11.333	-11.333	4.816	*

Bonferroni T table value = 2.36 (1 Tailed Value, P=0.05, df=30,4)

body weight change
File: 3717bwc Transform: NO TRANSFORMATION

BONFERRONI T-TEST - TABLE 2 OF 2 Ho:Control<Treatment

GROUP	IDENTIFICATION	NUM OF REPS	Minimum Sig Diff (IN ORIG. UNITS)	% of CONTROL	DIFFERENCE FROM CONTROL
1	0	10			
2	344	10	5.138	125.3	5.300
3	377	8	5.450	132.9	12.475
4	392	4	6.797	165.8	8.100
5	415	3	7.563	184.5	15.433

body weight change
File: 3717bwc Transform: NO TRANSFORMATION

WILLIAMS TEST (Isotonic regression model) TABLE 1 OF 2

GROUP	IDENTIFICATION	N	ORIGINAL MEAN	TRANSFORMED MEAN	ISOTONIZED MEAN

1	0	10	4.100	4.100	4.100
2	344	10	-1.200	-1.200	-1.200
3	377	8	-8.375	-8.375	-6.917
4	392	4	-4.000	-4.000	-6.917
5	415	3	-11.333	-11.333	-11.333

body weight change
File: 3717bwc Transform: NO TRANSFORMATION

WILLIAMS TEST (Isotonic regression model) TABLE 2 OF 2

IDENTIFICATION	ISOTONIZED MEAN	CALC. WILLIAMS	SIG P=.05	TABLE WILLIAMS	DEGREES OF FREEDOM
0	4.100				
344	-1.200	2.434	*	1.70	k= 1, v=30
377	-6.917	4.771	*	1.78	k= 2, v=30
392	-6.917	3.825	*	1.80	k= 3, v=30
415	-11.333	4.816	*	1.81	k= 4, v=30

s = 4.868
Note: df used for table values are approximate when v > 20.