

ANNEX	II
POINT ADDRESSED	5.8.2 Supplementary Studies on the Active Substance

1.2	TITLE:	Hemodynamic Effects of Roundup, Glyphosate and Surfactant in Dogs
1.3	REPORT NUMBER	Japan Journal of Toxicology 3:03-68.
1.4	LAB REPORT NO.	Not applicable.
1.5	CROSS REFERENCE	5.8.2/03
1.6	AUTHORS:	Report: Tai, T., Yamashita, M. and Wakimori, H. Summary: Hastings, C.E.
1.7	DATE OF REPORT:	1990
1.8	PUBLISHED:	Yes
2.1	TESTING FACILITY:	Univ. of Tsukuba
2.2	DATES OF EXPERIMENTAL WORK:	Published report, experimental dates not given.
3	OBJECTIVES	As Title
4.1	TEST SUBSTANCE:	3 test substances were used: Isopropylamine salt of glyphosate Surfactant Roundup Herbicide (410 mg/ml glyphosate)
4.2	SPECIFICATION	Test materials were not otherwise specified.
4.3	STORAGE STABILITY	Not performed as part of this study.
4.4	STABILITY IN VEHICLE	Not performed as part of this study.
4.5	HOMOGENEITY IN VEHICLE	Not performed as part of this study.
4.6	VALIDITY	Not applicable.
5	VEHICLE/SOLVENT	See Sections 12 and 13.
6	PHYSICAL FORM	See Sections 12 and 13.
7.1	METHOD:	No published method or guideline was referenced in the report.
7.2	JUSTIFICATION	Not applicable.

7.3	COPY OF METHOD	Description of method used is included in report. For summary see point 12 below.
8	CHOICE OF METHOD	Not applicable.
9	DEVIATIONS	Not applicable.
10.1	CERTIFIED LABORATORY	Not applicable.
10.2	CERTIFYING AUTHORITY	Not applicable.
10.3	GLP:	The publication did not reference whether or not GLP's were followed.
10.4	JUSTIFICATION	Not applicable.
11.1	GEP:	Not applicable.
11.2	TYPE OF FACILITY (official or officially recognized)	Not applicable.
11.3	JUSTIFICATION	Not applicable.
12	TEST SYSTEM:	

Beagle dogs weighing 10 to 15 kg from Nihon Nosan Kogyo Co., Ltd. were used. They were divided into three groups (isopropylamine salt of glyphosate, surfactant or Roundup herbicide) of 5 dogs each. Dogs were anesthetized with Nembutal and artificially ventilated. Pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP) were monitored via a catheter into the right femoral vein into a pulmonary artery. The left femoral artery was cannulated to monitor arterial blood pressure (AP), to measure blood concentrations of glyphosate and to analyze arterial blood gas concentrations. Electrocardiograms were monitored every 15 minutes. Cardiac output was determined by the thermodilution method after injection of 5 ml of saline. The following calculated values were also determined: Cardiac index (CI), Systemic vascular resistance index (SVRI), left ventricular stroke work index (LVSWI) and pulmonary vascular resistance index (PVRI).

The isopropylamine salt of glyphosate in water was continuously injected intravenously at the rate of 20 ml/hr. HR, MAP, Mean PAP (MPAP), PCWP, CVP and CO were recorded every 15 minutes for an hour. Glyphosate concentrations were analyzed at 15, 30, 45 and 60 minutes after injection. The surfactant in water (150 mg/ml) was continuously injected intravenously at a rate of 10 ml/hr until MPAP was reduced 50% of the control value. Roundup was administered intravenously at a rate of 10 ml/hr until MAP was reduced to 50% of control.

13 FINDINGS:

Isopropylamine Salt of Glyphosate

At 60 minutes after administration of glyphosate, the MAP rose to 193.8 ± 37.3 mm Hg compared to $145.8 \text{ mm} \pm 33.4$ Hg prior to treatment. At 60 minutes after initiation of treatment, MPAP rose by 85.9% to 23.8 ± 1 mm Hg. Also at 60 minutes, LVSWI rose. CVP and PCWP showed slight increases. HR, CO and SVRI did not change. Blood pH was slightly decreased and $p\text{CO}_2$ was slightly increased at 60 minutes after administration. The concentration of glyphosate in blood rose slowly over time and at 60 minutes after initiation was $1,246 \pm 170$ ppm. A total of 8.2 g of glyphosate was injected during the 60 min period.

Surfactant

MAP decreased 50% from control at 37 ± 15.3 minutes following initiation. At the time of 50% MAP: CO and LVSWI were reduced, CVP, PCWP and PVRI were increased and HR, MPAP and SVRI did not change. There were no changes in blood gases or pH.

Roundup

MAP decreased 50% from control at 40.6 ± 6.1 minutes after initiation. At the time of 50% MAP: CO and LVSWI were decreased and PCWP was increased. There were no changes in blood gases or pH. Glyphosate concentration at the 50% MAP timepoint was 763.3 ± 60.6 ppm. A total of 2.8 ± 0.4 g of glyphosate was administered to the dogs.

CONCLUSIONS:

Dose levels were chosen to simulate those seen in humans following intentional (suicide) ingestions of large amounts of Roundup herbicide. Glyphosate levels in blood following such ingestions have ranges from 923 to 3450 ppm. The average level of glyphosate in this study of 1250 ppm 60 minutes after administration closely approximates the suicide use situation. Glyphosate alone caused an increase in MAP. Glyphosate did not cause changes in heart rate or cardiac output. Glyphosate caused a decrease in blood pH. It could not be determined if this was due to the direct injection of an acid, or due a metabolic acidosis. The administration of the surfactant and the Roundup herbicide reduced the MAP, LVSWI and CO. Apparently the cardiac depression observed with suicide ingestions of Roundup herbicide is due to the surfactant rather than the active ingredient, glyphosate.

- 14 STATISTICS: Standard methods were used.
- 15 REFERENCES: Not applicable.
- 16 UNPUBLISHED DATA Not applicable.