Protocol # 1

1. A total of _8_ column "E" rabbits were utilized in this study.

2. Painful procedure:

Exposure to a paralytic agent that can cause breathing difficulties in high doses.

3. Justification:

Injection of the paralytic agent leads to muscle weakness and breathing difficulties. The use of analgesics after the administration of the agent is not feasible: First, analgesics, by reducing pain, may reduce clinical signs necessary to assess experimental effects of the toxin and candidate therapeutic compounds. Second, the use of anesthesia may compromise respiratory function and therefore confound our ability to identify whether candidate treatment drugs improve clinical signs and promote survival. In addition, anesthetized rabbits would require ventilatory support, which is not feasible in this type of study.

4. No federal regulations mandate this procedure.

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Protocol # 2

1. A total of _13__ column "E" nonhuman primates were utilized in this study.

2. Painful procedure: Agent Exposure

3. Justification:

This protocol requires exposure to potentially lethal doses of chemical agents in unanesthetized nonhuman primates to evaluate the toxicity of these agents and the efficacy of pretreatment, treatment, decontamination procedures. In addition it allows monitoring of behavioral performance after exposure, pre-treatment, and treatment. Agent exposure is thought to cause some pain and/or distress because of the intense physiological changes produced by these toxicants. We cannot pre-treat the animals with any analgesic medication as this would compromise the results of the study in determining the dose of the chemical agent that leads to behavioral deficits.

4. No federal regulations mandate this procedure.

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Protocol # 3

1. A total of _12___ column "E" nonhuman primates were utilized in this study.

2. Painful procedure: Agent Exposure

3. Justification:

This protocol requires exposure to potentially lethal doses of chemical agents in unanesthetized nonhuman primates to evaluate the toxicity of these agents and the efficacy of pretreatment, treatment, decontamination procedures. In addition it allows monitoring of behavioral performance after exposure, pre-treatment, and treatment. Agent exposure is thought to cause some pain and/or distress because of the intense physiological changes produced by these toxicants. We cannot pre-treat the animals with any analgesic medication as this would compromise the results of the study in determining the dose of the chemical agent that leads to behavioral deficits.

4. No federal regulations mandate this procedure.

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Protocol # 4

1. A total of _4_ column "E" nonhuman primates were utilized in this study.

2. Painful procedure:

This protocol requires exposures in unanesthetized subjects.

3. Justification:

This protocol requires the analysis of acute and chronic toxic signs. We cannot pre-treat the animals with any medication as this would compromise the results of the study in determining the exposure parameters that lead to physiological and behavioral changes.

4. No federal regulations mandate this procedure.

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Protocol # 5

1. A total of _13___ column "E" pigs were utilized in this study.

2. Painful procedure:

Nerve agent exposure may lead to convulsions followed by potential pain from muscle fasciculations and convulsions.

3. Justification:

Exposures to nerve agent potentially can cause some pain and/or distress as a result of the intense physiological changes (potential seizures and muscle pain that follows convulsions, gastrointestinal distress, etc.). Subjecting the animals to levels of nerve agent that reliably elicit these toxic effects is essential for the goals of this protocol to develop a model for evaluating medical countermeasures to alleviate these effects and to protect the brain from damage. Anesthetics (e.g., barbiturates, inhalation anesthetics) and analgesics (for example, anti-inflammatory drugs) for relief of pain or distress are known to exhibit protective effects on brain function. Some anesthetics are effective anticonvulsants and could block seizures on their own. Many analgesics can interact with the drugs to be tested and/or the toxicity of the nerve agent (e.g. by causing respiratory depression) and thus can complicate the outcome and interpretation of the results, particularly when death is a potential experimental endpoint. Since parameters such as the frequency and intensity of seizure activity and the time of death after the agent exposure are experimentally essential observations for the research described in this protocol, use of anesthetic or analgesic compounds to alleviate the nerve agent induced pain/distress (which could either accelerate or delay the timing of these outcomes) would compromise the quality and utility of the results obtained.

4. No federal regulations mandate this procedure.

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Protocol # 6

1. A total of _32___ column "E" pigs were utilized in this study.

2. Painful procedure:

Exposure to chemical agent and the development of pulmonary edema.

3. Justification:

Interfering with the natural progression of chemical agent-induced injury would compromise our ability to use the model to assess medical countermeasures and countermeasure strategies. Alleviation of pain via use of analgesics is very likely to influence the same physiological mechanisms as phosgene and any potential therapeutics. Any administration of analgesics or anti-inflammatory drugs to reduce discomfort will confound experimental results and potentially mask the true outcomes of experimental countermeasure strategies. Administration of anesthetics or tranquilizers may also have respiratory depressant effects that would be contraindicated in this model.

4. No federal regulations mandate this procedure.

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Protocol # 7

1. A total of _57___ column "E" pigs were utilized in this study.

2. Painful procedure:

Median Lethal Dose (MLD) determinations and evaluation of nerve agent treatments with no intervention for pain/distress that may result from the expected sequelae of exposure.

3. Justification:

Quantitative evaluation of nerve agent toxicity and of the efficacy of therapeutic countermeasures requires exposure to lethal doses of a nerve agent, but the administration of drugs to relieve pain or distress could lead to an erroneous evaluation of the toxicity of these agents and the efficacy of treatment or decontamination products.

4. No federal regulations mandate this procedure.

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Protocol # 8

1. A total of _10___ column "E" pigs were utilized in this study.

2. Painful procedure:

Twenty-four hour Median Lethal Dose determinations and evaluation of nerve agent decontamination products with no intervention.

3. Justification:

Quantitative evaluation of nerve agent toxicity and the efficacy of therapeutic countermeasures requires exposure to lethal doses of a nerve agent, but the administration of drugs to relieve pain or distress could lead to an erroneous evaluation of the toxicity of these agents and the efficacy of treatment or decontamination products.

4. No federal regulations mandate this procedure.

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