Health Canada
Pest Management Regulatory Agency

Santé Canada
Agence de réglementation de la lutte antiparasitaire

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PROPOSED REGISTRATION DECISION

UCARCIDE 250 Antimicrobial Glutaraldehyde

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OVERVIEW

Proposed Registration Decision for Glutaraldehyde

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*[1] and in accordance with the Pest Control Products Regulations, is proposing full registration for the sale and use of UCARCIDE 250 Antimicrobial and GLUTEX GQ1 Sanitizer, containing the technical grade active ingredient glutaraldehyde, for use in reducing the levels of microorganisms on hard surfaces found in animal production facilities and farm equipment such as poultry and turkey houses; swine housing and farrowing areas; barns and large animal buildings; hatchers; setters; as well as chick processing facilities, cages and vehicles used to transport animals.

An evaluation of available scientific information found that, under the approved conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

This overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on human health, environmental and value assessment of UCARCIDE 250 Antimicrobial and the end-use product GLUTEX GQ1 Sanitizer.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks[2] to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration. The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 As per subsection 28(1) of the *Pest Control Products Act*.

2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

Before making a registration decision on glutaraldehyde, the PMRA will consider all comments received from the public in response to this consultation document[4]. The PMRA will then publish a Registration Decision Document[5] on glutaraldehyde, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

What Is Glutaraldehyde?

Glutaraldehyde is an antimicrobial that inhibits the growth of microorganisms (e.g. bacteria, fungi and viruses) through the alteration of RNA, DNA and protein synthesis.

❖ Health Considerations

♦ Can Approved Uses of Glutaraldehyde Affect Human Health?

Glutaraldehyde is unlikely to affect your health when used according to the label directions.

People could be exposed to glutaraldehyde when handling and applying the product. When assessing health risks, the PMRA considers two key factors: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers).

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when products containing glutaraldehyde are used according to the label directions.

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4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

UCARCIDE 250 Antimicrobial and GLUTEX GQ1 Sanitizer were moderately to highly acutely toxic in laboratory animals, were corrosive to the eyes and skin of rabbits and are considered to be potential dermal and respiratory sensitizers. Consequently, the statements “Danger Poison”, “Corrosive to eyes and skin” and “Potential skin and respiratory tract sensitizer” are required on the labels for both products.

Glutaraldehyde did not cause cancer or effects on the nervous system in animals. When glutaraldehyde was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to glutaraldehyde than the adult animal. Health effects in animals given daily doses of glutaraldehyde over long periods of time included effects on the kidney and irritation at the site of first contact as well as death at very high doses. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests. Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

♦ Residues in Water and Food

The uses of glutaraldehyde associated with the end-use product GLUTEX GQ1 Sanitizer do not involve application to food.

♦ Risk in Residential and Other Non-Occupational Environments

Estimated risk for non-occupational exposure is not of concern. This is a commercial product.

♦ Workplace Risks From Handling GLUTEX GQ1 Sanitizer

Occupational risks are not of concern when GLUTEX GQ1 Sanitizer is used according to the proposed label directions, which include protective measures.

A risk assessment conducted for individuals handling and re-entering areas treated with GLUTEX GQ1 Sanitizer indicated that risk for adults is not of concern when the product is used according to the label directions.

Farmers and pesticide applicators mixing, loading and applying GLUTEX GQ1 Sanitizer can come in direct contact with GLUTEX GQ1 Sanitizer on the skin or through inhalation. Therefore, the label will specify that anyone mixing or loading GLUTEX GQ1 Sanitizer must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks and chemical-resistant footwear, eye protection and NIOSH-approved organic-vapour-removing cartridge with prefilter respirator during mixing, loading, application, clean-up and repair.

Workers re-entering areas treated with GLUTEX GQ1 Sanitizer could be exposed to glutaraldehyde. Given the nature of activities performed, skin contact with treated surfaces should be minimal. The label identifies specific measures to minimize exposure to these workers through inhalation (e.g. ventilation requirements, reference to occupational exposure limits established for glutaraldehyde).

❖ Environmental Considerations

♦ What Happens When Glutaraldehyde Is Introduced Into the Environment?

The end-use product containing glutaraldehyde will be used only on indoor surfaces; therefore, entry of glutaraldehyde into the environment is expected to be negligible.

❖ Value Considerations

♦ What Is the Value of Glutaraldehyde?

GLUTEX GQ1 is a sanitizer for non-food contact surfaces found in animal production facilities and farm equipment such as poultry and turkey houses; swine housing and farrowing areas; barns and large animal buildings; hatchers; setters; as well as chick processing facilities, cages and vehicles used to transport animals.

GLUTEX GQ1 Sanitizer offers a different chemistry over other types of sanitizers to help in reducing the levels of bacterial, fungal and viral pathogens that can have potentially devastating effects in animal production facilities. GLUTEX GQ1 Sanitizer is not intended for use on food or feed, or in premises where food is prepared, manufactured or kept.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Key Risk-Reduction Measures

- **Human Health**

Because there is a concern with users coming into direct contact with GLUTEX GQ1 Sanitizer on the skin or through inhalation, anyone mixing or loading GLUTEX GQ1 Sanitizer must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks and chemical-resistant footwear, eye protection and NIOSH-approved organic-vapour-removing cartridge with prefilter respirator during mixing, loading, application, clean-up and repair.

Persons re-entering areas treated with GLUTEX GQ1 Sanitizer could be exposed to glutaraldehyde through inhalation; therefore, treated areas must be ventilated prior to re-entry. The label also refers to occupational exposure limits established for glutaraldehyde.

Next Steps

Before making a registration decision on glutaraldehyde, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Registration Decision Document, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and the Agency's response to these comments.

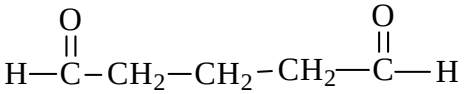
Other Information

At the time the PMRA makes its registration decision, it will publish an Evaluation Report on glutaraldehyde (based on the Science Evaluation section of this consultation document). In addition, the test data on which the decision is based will also be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

SCIENCE EVALUATION

1.0 The Technical Grade Active Ingredient, its Properties and Uses

1.1 Identity of the Technical Grade Active Ingredient

Active ingredient		Glutaraldehyde
Function		Biocide
Chemical name		
1.	International Union of Pure and Applied Chemistry (IUPAC)	1,5-pentanedial
2.	Chemical Abstracts Service (CAS)	1,5-pentanedial
CAS number		111-30-8
Molecular formula		$C_5H_8O_2$
Molecular weight		100.2 g/mol
Structural formula		
Purity of the technical grade active ingredient		48.5% minimum

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product— Glutaraldehyde (UCARCIDE 250 Antimicrobial)

Property	Result
Colour and physical state	Colourless to straw yellow
Odour	Fruity
Melting range	Not applicable
Boiling point or range	101°C
Density (g/mL)	1.1267 at 20°C

Property	Result	
Vapour pressure at 20°C	11.5 mm Hg	
Henry's law constant at 20°C	5.246×10^{-2}	
Ultraviolet (UV)—visible spectrum	No absorbance at $\lambda > 300$ nm.	
Solubility in water at 20°C	Completely soluble	
Solubility in organic solvents at 20°C (g/100 mL)	**Solvent** Dichloromethane Ethyl acetate n-Hexane Toluene Fully soluble in acetone and isopropanol	**Solubility** 70 59 0.19 8.5
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} at 25°C = –0.33	
Dissociation constant (pK_a)	No dissociable groups	
Stability (temperature, metal)	Polymerizes at elevated temperature. Stable to sunlight and metals.	

End-Use Product—GLUTEX GQ1 Sanitizer

Property	Result
Colour	Transparent colourless to pale yellow
Odour	Sharp, fruity medicinal odour
Physical state	Liquid
Formulation type	Solution
Guarantee	Glutaraldehyde, 14.0% minimum Alkyl (40% C12, 50% C14, 10% C16) dimethyl benzyl ammonium chloride, 2.5% minimum
Container material and description	High density polyethylene with ultraviolet light protection
Density	1.035 g/cm^3 at 20°C

Property	Result
pH of 1% solution in water	3.5 at 20°C
Oxidizing or reducing action	Compatible with oxidizing and reducing reagents used in industrial water treatment systems.
Storage stability	Shown to be stable for more than one year when stored at ambient temperature
Explodability	The product does not have any explosive properties.

1.3 Directions for Use

GLUTEX GQ1 Sanitizer is a sanitizer for non-food contact surfaces found in animal production facilities and farm equipment such as: poultry and turkey houses, swine housing and farrowing areas, barns and large animal buildings, hatchers, setters, and chick processing facilities, cages and vehicles used to transport animals. The relevant parameters for treatment are supported by data (Table 1.3.1).

Table 1.3.1 Treatment parameters supported by data

Treatment Solution	Method of Application	Contact time
3.7–7.3 mL GLUTEX GQ1 Sanitizer per litre of water (600–1200 ppm a.i.)	Mop, spray or immersion.	5 minutes

1.4 Mode of Action

GLUTEX GQ1 Sanitizer contains two active ingredients with different modes of action. The biocidal activity of glutaraldehyde is a consequence of its alkylation of sulfhydryl, hydroxyl, carboxyl and amino groups of microorganisms, which alters RNA, DNA and protein synthesis. Alkyl (40% C12, 50% C14, 10% C16) dimethyl benzyl ammonium chloride (ADBAC) targets the cytoplasmic membrane of microorganisms, inactivates energy-producing enzymes and denatures cell proteins.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Technical Grade of Active Ingredient

A validated capillary gas chromatography (GC) method was provided for the determination of glutaraldehyde. Based on the validation data and the chromatograms provided, the method was assessed to be sufficiently specific, precise and accurate.

2.2 Method for Formulation Analysis

Gas chromatography and titration methods were submitted for the determination of glutaraldehyde and the quaternary ammonium chloride, respectively. The methods were found to be acceptable for the respective determinations.

2.3 Methods for Residue Analysis

Not applicable.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for the antimicrobial glutaraldehyde was conducted. Although studies covering most of the required data were submitted, many of the studies were non-guideline and unacceptable because of design and reporting limitations and thus considered supplementary. However, the information provided was considered adequate in its entirety to characterize the hazards associated with potential glutaraldehyde exposure.

The toxicokinetics and metabolism of glutaraldehyde was evaluated in rats and rabbits following both dermal application and intravenous injection of single doses of glutaraldehyde. Approximately 5% to 9% of the administered dose was absorbed following a single 24-hour dermal application of glutaraldehyde to rats, compared to 10% to 30% following dermal application to rabbits. Plasma levels for the dermally dosed animals were roughly 100 to 1000-fold lower than those for animals receiving the same amount of glutaraldehyde via intravenous injection. Following intravenous administration, glutaraldehyde was rapidly eliminated, predominantly via expired air. Elimination was less rapid following dermal administration due to the absorption phase through the skin and occurred primarily via the urine. When glutaraldehyde was applied dermally, the skin retained a large proportion of the administered dose. Higher doses of glutaraldehyde resulted in longer terminal half-lives in plasma compared to lower doses, indicating that a saturation of the elimination processes was occurring. Tissue burdens of radioactivity were relatively low following both dermal and intravenous administration. Metabolism of glutaraldehyde likely involves oxidation to glutaric semialdehyde, followed by further oxidation to glutaric acid and subsequent degradation to carbon dioxide.

In acute toxicity studies, glutaraldehyde was highly toxic by the oral route and moderately toxic by the dermal and inhalation routes. Results from irritation studies with glutaraldehyde showed that it is corrosive to both eyes and skin. Glutaraldehyde was sensitizing in a dermal sensitization study conducted using the local lymph node assay. In a study conducted to determine the potential for glutaraldehyde to induce a sensitization response of the respiratory tract, levels of immunoglobin E (IgE) were increased in mice following dermal exposure to glutaraldehyde, demonstrating that glutaraldehyde is a likely respiratory sensitizer. Information from the public literature indicates that occupational exposure to glutaraldehyde results in allergic contact dermatitis as well as a wide range of respiratory symptoms, including asthma and rhinitis.

Physiological evidence that glutaraldehyde induces asthma in health care workers at exposures within regulated limits has been documented (Di Stefano et al. 1999).

The end-use product, GLUTEX GQ1 Sanitizer, was of moderate acute toxicity by the oral and inhalation routes, of low acute toxicity via the dermal route, and corrosive to both eyes and skin. As no dermal sensitization study conducted with GLUTEX GQ1 Sanitizer was provided, and because both active ingredients (glutaraldehyde and ADBAC) are known to be sensitizing to the skin, the end-use product will be considered a potential dermal sensitizer. There are no formulants of toxicological concern in the end-use product.

In subchronic and chronic toxicity studies, glutaraldehyde-induced toxicity occurred primarily at the site of first contact in the form of non-neoplastic lesions of the respiratory tract following inhalation, irritation of the gastrointestinal tract following ingestion, and irritation and necrosis of the skin following dermal application. When glutaraldehyde was administered via the drinking water, decreased water consumption was consistently noted, which was likely due to an aversion to the taste of the dosing solution. This reduced water consumption often resulted in body weight depressions and urinary effects such as decreased urinary volume and increased urinary osmolality and specific gravity.

Effects on the kidney were evident in several studies, including the 90-day drinking water studies in the mouse and the dog, the 13-week inhalation studies in the rat and mouse, and the two-year drinking water study in the rat. Renal toxicity was manifest in these studies as increased kidney weight, kidney mineralization, increased levels of blood urea nitrogen, kidney tubular basophilia, kidney tubular pigmentation, and interstitial nephritis. Dogs appeared to be more sensitive to kidney effects than mice, with increased kidney weights occurring at approximately 9 mg/kg bw/day in the dog but at much higher doses (i.e. 200 mg/kg bw/day) in the mouse following a similar duration of dosing.

The 28-day dermal toxicity study in the rat revealed systemic effects, evident as increased levels of both platelets and blood urea nitrogen, that were considered to be secondary to the severe irritation noted in test animals.

Immune responses believed to be secondary to severe stress and irritation were noted in several studies, and included effects on the lymph nodes (ectasia, histiocytosis, swelling, lymphoid and cellular depletion), thymus (decreased weight, atrophy), and spleen (pale in appearance, lymphoid depletion, increased size).

A number of parameters were affected in several species following exposure to glutaraldehyde for varying durations that suggest a possible interaction with endocrine systems. These effects included glandular ectasia of the uterus, uterine polyps, ovarian cysts, decreased testes size, change in the consistency of the testes, seminiferous tubule degeneration, decreased epididymal weight, and changes in the estrous cycle. However, these findings occurred at doses that elicited severe signs of toxicity, indicating that the health of the animals was already compromised.

Mortality was noted in several short-term and long-term inhalation studies and in the rabbit developmental toxicity study. In rats exposed via inhalation for nine days, mortality was noted following six exposures to glutaraldehyde at 2.0 ppm. In the two-week studies, mortality was noted between four and nine days of exposure to glutaraldehyde at 5 ppm in rats and at 1.6 ppm in mice. Mice were more sensitive than rats to the effects of glutaraldehyde following inhalation exposure, with mortality occurring at lower doses among mice compared to rats. The mortality among mice was attributed to obstruction of their airways caused by glutaraldehyde-induced nasal lesions. Mice are more susceptible than rats to obstruction of the nasal passageways because mice generally have smaller respiratory passageways. Deaths were noted in mice exposed via inhalation to glutaraldehyde at 0.5 ppm and 1.0 ppm during the first three weeks of exposure in the 13-week study. Mortality occurred at higher doses in the two-week inhalation study with mice, providing evidence that increased toxicity may occur with increased duration of exposure. Administration of glutaraldehyde via gavage at 45 mg/kg bw/day resulted in mortality in the rabbit developmental toxicity study. No mortality was noted when glutaraldehyde was administered via the drinking water at doses up to 68 mg/kg bw/day in the rat developmental toxicity study, 98 mg/kg bw/day in the multigeneration rat reproduction study, 86 mg/kg bw/day in the chronic toxicity study in rats, and 238 mg/kg bw/day in the 90-day mouse study. In the rabbit developmental toxicity study, deaths occurred at 45 mg/kg bw/day shortly after the initiation of dosing (i.e. deaths occurred during gestation days 9 and 11 while animals were dosed between gestation days 7 and 19). This dose, however, was close to the acute oral LD_{50} for glutaraldehyde.

In the two-year drinking water study with Fischer 344 rats, large granular lymphocytic (LGL) leukemia, a common and spontaneously occurring neoplasm in this strain of rat, was found at sites in the spleen, liver, lungs and ovaries of female rats at higher incidence than both historical and concurrent control values. Statistical analyses indicated that the incidence of LGL leukemia was significantly increased in all groups of female rats relative to control. Moreover, there was an association between the dose of glutaraldehyde and the severity and grade of leukemia observed in the spleen of female rats. However, it was concluded that the increased incidence of LGL leukemia in female F344 rats appeared to be a sex- and strain-specific (i.e., a second drinking water study using Wistar rats did not provide evidence for carcinogenicity) and route-specific (i.e., chronic exposure of F344 rats to glutaraldehyde via inhalation did not lead to neoplastic lesions) effect. Therefore, a cancer risk assessment for Glutaraldehyde was not required.

Evidence of genotoxic potential was demonstrated in the database, as glutaraldehyde induced point mutations in bacterial and mammalian cells, chromosome aberrations and sister chromatid exchanges in vitro. In in vivo assays, glutaraldehyde caused damage to the chromosomes and to the mitotic apparatus of erythrocytes when injected intraperitoneally, but not when administered orally or via inhalation. Glutaraldehyde was not associated with unscheduled DNA synthesis in vitro.

There was no evidence of teratogenicity in the developmental toxicity studies in rats and rabbits, and glutaraldehyde did not affect the standard reproductive indices (mating, gestation, fertility, viability) in a two-generation rat reproduction study. Fetotoxicity (decreased pup and litter weights) and developmental toxicity (increased early resorptions, increased postimplantation

loss, and decreased fetal weight) were noted. These effects were likely secondary to maternal toxicity as they occurred at dose levels where maternal animals exhibited signs of systemic toxicity, such as lower body weight gains and mortality.

Overall, there is evidence in the database that female animals were more sensitive to the effects of glutaraldehyde than males. For instance, body weight effects were noted only in female animals from the 90-day drinking water study in the mouse, and were more severe or occurred at lower doses in females than in males from the two-week inhalation studies with rats and mice. A similar trend was noted in the two-year inhalation study in rats, where females showed increased mortality and decreased body weight at a dose where mortality and body weight were not affected in males. Furthermore, nasal lesions were noted in females but not in males at the lowest doses tested in the 13-week and two-year inhalation studies with mice. Also, kidney effects were restricted to females in the 90-day drinking water study with dogs. Conversely, in the 9-day and 13-week inhalation studies in the rat, effects on body weight were noted in males at lower doses than in female rats. It is likely that the differential in effects between male and female animals is due to the fact that, in many studies, the actual dose (on a mg/kg bw basis) administered to female animals was higher than the dose administered to males.

3.2 Determination of Acceptable Daily Intake

The proposed uses do not include application to food; therefore the establishment of an acceptable daily intake (ADI) is not required.

3.3 Determination of Acute Reference Dose

The proposed uses do not include application to food; therefore the establishment of an acute reference dose (ARfD) is not required.

3.4 Occupational and Bystander Risk Assessment

3.4.1 Toxicological Endpoints

For occupational exposure by the dermal route, the NOAEL of approximately 3 mg/kg bw/day from the 90-day drinking water study in the dog was considered appropriate to use in the risk assessment. In this study, vomiting, decreased water consumption, and kidney effects (i.e. increased relative weight, mineralization) were noted at the LOAEL of approximately 10 mg/kg bw/day. This study is considered adequate to protect for any possible systemic effects of glutaraldehyde, as the dog was determined to be the most sensitive species for kidney effects. The recommended margin of exposure (MOE) is 300, with the standard uncertainty factor of 100 to account for intraspecies variability and interspecies extrapolation, and an extra uncertainty factor of 3 for the use of a short-term study for a chronic risk assessment. With evidence in the database of increasing toxicity with increased duration of exposure, the extra uncertainty factor is to account for unknown durational effects that may be noted following chronic exposure.

The 28-day dermal study in the rat was deemed to be inadequate for a chronic risk assessment because of the short duration of the study. Furthermore, no NOAEL was established in this study and the LOAEL was based on severe skin irritation and necrosis. Direct systemic toxicity was not evident in this study.

From the studies available, there is not enough information to determine a threshold concentration for dermal irritation. In the 14-day dermal study in the mouse, a 0.5% solution of glutaraldehyde in water did not cause irritation; however, this study is a range-finding study and has limitations. Severe irritation and necrosis were noted at the LOAEL in the 28-day dermal study in the rat, where a 2.5% solution of glutaraldehyde was used. Furthermore, a 1% solution did not produce necrosis of the skin in the dermal irritation study in the rabbit, but other signs of dermal irritation were noted with this concentration. The toxicology database does not provide information relating to any possible systemic effects that would result following repeated dermal exposures to a non-irritating concentration of glutaraldehyde. Therefore, in order to protect for possible systemic toxicity caused by exposure to glutaraldehyde, the systemic endpoints noted following oral exposure in the dog will be used for the risk assessment.

The NOAEL of 3 mg/kg bw/day from the 90-day drinking water study in the dog compares to the NOAEL of 4.3/6.7 mg/kg bw/day for males/females from the multigeneration reproduction study in the rat, where encrustation of the eyes and dental abnormalities were noted in parental females at the LOAEL of 28.3 mg/kg bw/day. The rabbit developmental study gave a NOAEL of 15 mg/kg bw/day with mortality at the LOAEL of 45 mg/kg bw/day, a dose approaching an acutely toxic dose.

For occupational exposure by the inhalation route, the 13-week inhalation study in the rat was deemed to be the most appropriate study for use in the risk assessment. This study provided the lowest NOAEL of the database (0.024 mg/kg bw/day) and is deemed adequate to protect for irritation of the respiratory tract that is expected to occur following inhalation exposure. Although several parameters were not assessed in this study (i.e. several tissues were not collected for histological examination, several organs were not weighed), these endpoints were examined in the other 13-week study and in the two-year inhalation study with the rat. Although the two-year rat inhalation study was missing haematology and clinical chemistry measurements, these were conducted in the 13-week studies. When all of the inhalation studies are combined, all relevant endpoints were assessed.

Effects were noted at the lowest dose tested in many of the inhalation studies, and some variability exists among the NOAELs and LOAELs established in the inhalation studies of similar durations. Therefore, the lowest NOAEL from the inhalation studies was selected for the risk assessment and is considered to be protective of adverse effects following inhalation exposure. This NOAEL also protects for systemic toxicity and mortality noted at higher doses in the other inhalation studies. An MOE of 100 was considered adequate for the risk assessment, with the standard uncertainty factor of 100 to account for intraspecies variability and interspecies extrapolation.

Although an endpoint from a sub-chronic study is being used for a chronic risk assessment, an extra uncertainty factor of 3 was not deemed to be necessary for extrapolation to chronic exposure effects in the inhalation exposure risk assessment because the database contains chronic inhalation studies in which effects occurred at higher doses. Therefore, as there is no uncertainty regarding toxic effects from chronic inhalation exposure to glutaraldehyde, the NOAEL from the 13-week inhalation study is considered to be the most protective, regardless of duration of exposure.

3.4.1.2 Dermal Absorption

A dermal absorption value of 14% was used in the exposure and risk assessment. The dermal absorption value was selected based on a dermal pharmacokinetic study conducted in rats and rabbits (PMRA #1280144). Two major limitations of this study were that a skin wash was not performed prior to sacrifice and there was total occlusion of the application site. In rats, low total recovery of the dermally administrated dose was observed. Dermal absorption values were calculated from the sum of the corrected doses in urine, faeces, cage washes, expired CO_2, tissues and carcass. The residues in the skin were not included as absorbed dose as these values were considered to be unrealistic due to poor study design. Glutaraldehyde has a low log K_{ow} of −0.33 and is volatile. Thus, based on its physical/chemical properties, skin residues of glutaraldehyde would be expected to be low in field conditions.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/Loader/applicator Exposure and Risk

3.4.2.1.1 Dermal Exposure

There is potential for intermittent, long-term exposure to glutaraldehyde during mixing, loading and applying GLUTEX GQ1 Sanitizer. Dermal exposure estimates for workers spraying GLUTEX GQ1 Sanitizer were generated from data in the Pesticide Handler Exposure Database (PHED). PHED version 1.1 is a compilation of generic M/L/A passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. With few exceptions, the PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group (NAFTA TWG) on Pesticides.

Application methods considered in this assessment for GLUTEX GQ1 Sanitizer are high pressure and low pressure equipment.

Dermal exposure was estimated by coupling the unit exposure values with the amount product handled per day and the dermal absorption value. Exposure was normalized to a 70 kg body weight.

Exposure estimates were compared to the NOAEL of 3 mg/kg/day from the 90 day oral dog study to obtain the margin of exposure (MOE); the target MOE is 300.

Table 3.4.1 Mixer/Loader/Applicator Dermal Exposure Estimates and MOE

PPE Scenario	Application Method	Total Dermal Unit Exposure (µg/kg ai handled)	Rate (kg ai/L)	Default, Volume Handled/Day (L/day)	Dermal Exp. Estimates (mg ai/kg bw/day)[a]	Dermal MOE[b]
Coveralls over single layer, gloves	High pressure equipment	2453.52	0.00102	940	0.004704	637

[a] Dermal Exposure Estimates =
PHED Exposure (µg ai/kg ai handled) × Rate (0.00102 kg ai/L) × Volume handled (L/day) × Dermal Absorption Factor (14%) × mg/1000 µg
bw (70kg)

[b] MOE_{Dermal} = NOAEL Dermal (3mg/kg bw/day), target 300
Dermal exposure estimates (mg/kg/day)

The target MOE is achieved with coveralls over single layer and gloves for application with high pressure equipment. The dermal exposure and risk assessment for application with low pressure equipment is considered to be covered off by the exposure and risk assessment for high pressure equipment.

3.4.2.1.2 Inhalation Exposure

Inhalation exposure was estimated by coupling the unit inhalation exposure values (17 LPM for light work) from PHED with the amount product handled. Exposure was normalized to a 70 kg body weight. Inhalation exposure estimates (µg ai/kg bw/day) were coupled with a NOAEL of 0.024 mg/kg/day from 13-week inhalation study in the rat to obtain the margin of exposure (MOE). The target MOE is 100.

Table 3.4.2 Mixer/Loader/Applicator Inhalation Exposure Estimates and MOEs with Respirator

Application Method	Total Inhalation Unit Exposure (µg/kg ai handled)	Rate (kg ai/L)	Default, volume handled/day (L/day)	Inhalation Daily Exposure Estimates (mg ai/kg bw/day)[a]	Inhalation MOE[b]
High pressure equipment	15.1	0.00102	940	0.000207	115

[a] Inhalation Exposure Estimates =
PHED Exposure (µg ai/kg ai handled) × Rate (0.00102 kg ai/L) × Volume handled (L/day) × 0.1 respiratory protection factor × mg/1000 µg
bw (70 kg)

[b] MOE_{Dermal} = NOAEL Inhalation (0.024mg/kg bw/day), target 100
Inhalation Daily Dose (mg/kg/day)

The target MOE is achieved with a NIOSH approved respirator, which provides 90% protection. The inhalation exposure and risk assessment for low pressure equipment is considered to be covered by the exposure and risk assessment for high pressure equipment.

Furthermore, use of a respirator has merit given that the end-use product has been identified as a potential respiratory sensitizer.

3.4.2.2 Postapplication Worker Exposure and Risk

There is potential for exposure to workers re-entering areas treated with GLUTEX GQ1 Sanitizer. Areas include farms, poultry and turkey houses, laying houses, swine production and housing, barns, large animal building, hatchers, setters, chick processing facilities, trucks and other animal vehicles. Given the nature of activities performed, dermal contact with treated surfaces should be minimal. Given the indoor applications, there is potential for exposure through inhalation and this is addressed by exposure reduction measures on the label (e.g. ventilation requirements, reference to occupational exposure limits established for glutaraldehyde).

3.4.3.3 Bystanders Exposure and Risk

This is a commercial product used in commercial settings; bystander exposure is considered negligible. Therefore, health risk to bystanders is not of concern.

3.5 Food Residues Exposure Assessment

No food uses were associated with the proposed end-use product; therefore a dietary exposure assessment was not conducted.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental releases of glutaraldehyde are expected to be negligible as the end use product containing glutaraldehyde will be used only on indoor surfaces.

4.2 Effects on Non-Target Species

Considering the end use product is for indoor use only, there will be negligible exposure of non-target organisms in the environment.

5.0 Value

5.1 Effectiveness Against Pests

Data from three different sets of laboratory trials were submitted. Each of these studies was found to have an appropriate experimental design. The test methods and organisms are listed below:

- Sanitizer Test for Non-Food Contact Surfaces against *Klebsiella pneumonia* ATCC 4352, *Salmonella cholerasuis* ATCC 10708, *Staphylococcus aureus* ATCC 6538 and *Pseudomonas aeruginosa* ATCC 15442

  Performance standard: The results must show a bacterial reduction of at least 99.9% over the parallel control count within 5 minutes.

- Sanitizer Test for Non-Food Contact Surfaces against *Aspergillus fumigatus* ATCC 24547

  Performance standard: The results must show a bacterial reduction of at least 99.9% over the parallel control count within 5 minutes.

- USEPA DIS/TSS-7 which is similar to the virucidal test proposed in PMRA's T-1-215 against Infectious Bursal Disease Virus (IBDV) strain 2512 and the Avian Influenza/Turkey/Wisconsin virus, SARS-associated Coronavirus, Porcine Circovirus and Pathogenic Avian Influenza Virus (HPAI, H5N1)

  Performance standard: The product must demonstrate complete inactivation of the virus at all dilutions. When cytotoxicity is evident, at least a 3-log reduction in titer must be demonstrated beyond the cytotoxic level.

GLUTEX GQ1 Sanitizer met the sanitizer and virucide performance standard in all above mentioned tests.

5.1.1 Acceptable Efficacy Claims

The submitted data demonstrated that GLUTEX GQ1 Sanitizer effectively reduced levels of bacteria, fungi and viruses when applied at rates of 3.7–7.3 mL of product per litre of water (600–1200 ppm of active ingredients).

5.2 Phytotoxicity to Host Plants

Not applicable.

5.3 Impact on Succeeding Crops

Not applicable.

5.4 Economics

No information provided.

5.5 Sustainability

5.5.1 Survey of Alternatives

Very few currently registered sanitizers can be used in animal production facilities and on farm equipment. The registration of GLUTEX GQ1 Sanitizer may provide an advantage over other types of sanitizers by offering a different chemistry to help in reducing the levels of bacterial, fungal and viral pathogens that can have potentially devastating effects in animal production facilities.

The key options available for sanitizing animal production facilities and farm equipment are summarized in Table 4 of Appendix I. Some products have very generic claims and could be used in animal production facilities and on farm equipment, but may not have been evaluated for those specific uses. It should noted that there could be disinfectants registered under the *Food and Drugs Act* that could potentially be used in such premises.

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

Not applicable.

5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Results from the data submitted as part of the literature review on resistance to glutaraldehyde and alkyl (40% C12, 50% C14, 10% C16) dimethyl benzyl ammonium chloride showed that the microorganisms tested had a general tendency to become more tolerant to various biocides, including glutaraldehyde and alkyl (40% C12, 50% C14, 10% C16) dimethyl benzyl ammonium chloride, as exposure time to sub-lethal concentrations increased. However, this experiment was conducted at concentrations of active ingredients well bellow those recommended on the proposed label. As a result, the change in susceptibility to the active ingredients observed in laboratory is unlikely to have an impact at the operational level

5.5.4 Contribution to Risk Reduction and Sustainability

Not applicable.

6.0 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, glutaraldehyde was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of glutaraldehyde were also considered, including major transformation products formed in the environment, microcontaminants in the technical product and formulants in the end-use product GLUTEX GQ1 Sanitizer. The PMRA has reached the following conclusions:

- Glutaraldehyde does not meet the Track 1 criteria for persistence or bioaccumulation. Glutaraldehyde is expected to be readily biodegradable in water, sediment and soil. Its log *n*-octanol–water partition coefficient was estimated to be -0.33, which indicates that glutaraldehyde is not expected to bioaccumulate. Glutaraldehyde does not meet the Track 1 criteria; therefore, it is not classified as a Track 1 substance.

- Technical grade glutaraldehyde does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

- The end-use product GLUTEX GQ1 Sanitizer and UCARCIDE 250 Antimicrobial do not contain any formulants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

Therefore, the use of glutaraldehyde is not expected to result in the entry of Track 1 substances into the environment.

7.0 Summary

7.1 Human Health and Safety

Both glutaraldehyde and the associated end-use product, GLUTEX GQ1 Sanitizer, are corrosive to eyes and skin, and are potential sensitizers of the skin. The information provided as well as information contained in the public literature suggest that glutaraldehyde is a potential sensitizer of the respiratory tract. However, it is not known with certainty at what exposure level glutaraldehyde can induce a sensitization response in the skin or the respiratory tract.

Exposure to glutaraldehyde via inhalation results in mortality among laboratory animals. Limited systemic toxicity was noted following repeated dermal and inhalation exposures. Following short-term and chronic oral exposure, kidney effects were noted in the form of increased weights, mineralization, interstitial nephritis, tubular pigmentation, and tubular basophilia. Due to the corrosiveness of glutaraldehyde, irritation at the site of first contact was a consistent finding within the toxicology database. Lesions of the respiratory tract and severe skin irritation with necrosis were noted following repeated exposure via the inhalation and dermal routes, respectively.

No evidence of neurotoxic potential was demonstrated in the database. Glutaraldehyde is not a developmental or reproductive toxicant. No increased susceptibility of fetuses to in utero exposure to glutaraldehyde was demonstrated in the developmental toxicity studies conducted with rats and rabbits.

There is some evidence for a significant increase in toxicity with increased duration of exposure via inhalation in mice. There is also some evidence indicating a sex-specific sensitivity to the effects of glutaraldehyde, with females being more sensitive than males, but this observation may be driven by the fact that actual doses administered to females were higher than the doses administered to males.

Mixer, loader, applicators handling GLUTEX GQ1 Sanitizer and workers re-entering treated areas are not expected to be exposed to levels of GLUTEX GQ1 Sanitizer that will result in unacceptable risk when the product is used according to label directions

7.2 Environmental Risk

Glutaraldehyde is for use on indoor surfaces and will not be released to the environment, therefore non-target organisms will not be exposed.

7.3 Value

The data submitted to register GLUTEX GQ1 Sanitizer are adequate to demonstrate its efficacy for use as a sanitizer in animal production facilities and on farm equipment. GLUTEX GQ1 Sanitizer offers a different chemistry, over other types of sanitizers, to help in reducing the levels of bacterial, fungal and viral pathogens which can have potentially devastating effects in animal production facilities.

7.4 Unsupported Uses

The application of GLUTEX GQ1 Sanitizer by fogging or atomizing for treatment of air and surfaces was not supported by the PMRA because the studies were not conclusive. The test method used for air monitoring was not considered appropriate and it was unclear whether fogging would meet the performance standard required for a sanitizer as it was not tested in a laboratory test. Unsupported uses are outlined in Table 5 of Appendix I.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of the technical grade active ingredient glutaraldehyde (UCARCIDE 250 Antimicrobial) and the end-use product GLUTEX GQ1 Sanitizer to effectively reduce levels of bacteria, fungi and viruses that can be potentially found in animal housing facilities. An evaluation of current scientific data from the applicant, scientific reports and information from other regulatory agencies has resulted in the determination that, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

a.i.	active ingredient
ADBAC	alkyl (40% C12, 50% C14, 10% C16) dimethyl benzyl ammonium chloride
ADI	acceptable daily intake
ARfD	acute reference dose
ATCC	American Type Culture Collection
bw	body weight
CAS	chemical abstracts service
DNA	deoxyribonucleic acid
F	females
g	gram
GC	gas chromatography
HDT	highest dose tested
Hg	mercury
IgE	immunoglobin E
IBDV	Infectious Bursal Disease Virus
IUPAC	International Union of Pure and Applied Chemistry
i.v.	intravenous
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LGL	large granular lymphocyte
LOAEL	lowest observed adverse effect level
mg	milligram
mL	millilitre
mm	millimetre
M	males
MAS	maximum average score
MOE	margin of exposure
nm	nanometre
N/A	not applicable
NAFTA TWG	North American Free Trade Agreement Technical Working Group
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
NZW	New Zealand white
PHED	Pesticide Handler Exposure Database
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RNA	ribonucleic acid
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Acute Toxicity of Glutaraldehyde Technical and Its Associated End-use Product (GLUTEX GQ1 Sanitizer)

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Glutaraldehyde Technical				
Oral	Rat	LD_{50} = 123 mg/kg bw in M LD_{50} = 77 mg/kg bw in F LD_{50} = 100 mg/kg bw in M & F	HIGH TOXICITY	1158496
Oral	Rat	LD_{50} = 65-162 mg/kg bw	HIGH TOXICITY	1131527
Dermal	Rabbit	LD_{50} = 759-2000 mg/kg bw	MODERATE TOXICITY	1218836
Dermal	Rabbit	LD_{50} = 1006-2493 mg/kg bw	SLIGHT TOXICITY	1218841
Inhalation	Rat	LC_{50} = 0.096 mg/L in M LC_{50} = 0.164 mg/L in F	MODERATE TOXICITY	1218843
Inhalation	Rat	LC_{50} > 0.01-0.07 mg/L	MODERATE TOXICITY	1147991
Inhalation	Rat	LC_{50} = 0.11-0.18 mg/L	MODERATE TOXICITY	1173340
Inhalation	Rat	LC_{50} > 0.02 mg/L in F	HIGH TOXICITY	1218845
Skin irritation	Rabbit	MAS[a] = 4.5	Corrosive	1218848
Eye irritation	Rabbit	Scoring system not known; MAS could not be calculated.	Slightly to moderately irritating	1218836
Eye irritation	Rabbit	Scoring not possible due to severe corneal opacity.	Corrosive	1218848
Skin sensitization (LLNA)	Mouse	Positive	Potential dermal sensitizer	1158494
Respiratory sensitization (IgE)	Mouse	Positive	Potential respiratory sensitizer	1158494
Acute Toxicity of End-Use Product: GLUTEX GQ1 Sanitizer				
Oral	Rat	LD_{50} = 1205 mg/kg bw in M LD_{50} = 911 mg/kg bw in F LD_{50} = 1051 mg/kg bw in M & F	MODERATE TOXICITY	875632
Dermal	Rabbit	LD_{50} > 2000 mg/kg bw	LOW TOXICITY	875632
Inhalation	Rat	LC_{50} > 0.228 mg/L	MODERATE TOXICITY	1173771
Skin irritation	Rabbit	MAS = 4.9	Corrosive	875632
Eye irritation	Rabbit	Scoring not possible due to severe corneal opacity.	Corrosive	875632
Skin sensitization	Data requirement waived as both active ingredients are known dermal sensitizers		Sensitizer	N/A

[a] MAS = maximum average score for 24, 28 and 72 hours

Table 2 Toxicity Profile of Glutaraldehyde

Study Type	Species	Results[a] (mg/kg/day)	Reference
90-day drinking water	Mouse	NOAEL and LOAEL could not be established as study was considered supplemental (histopathology was not assessed at all doses). Effects were noted in F at 31 mg/kg bw/day, the lowest dose tested, and included decreased body weight gain.	1131529
90-day drinking water	Dog	**NOAEL:** 3.3/3.2 mg/kg bw/day in M/F. **LOAEL:** 9.6/9.9 mg/kg bw/day in M/F, based on vomiting; reduced water consumption in M; and hypocalcemia, increased relative kidney weight, and kidney mineralization in F.	1142317
28-day dermal	Rat	**Systemic toxicity NOAEL:** 150 mg/kg bw/day. **Systemic toxicity LOAEL:** not established as no adverse systemic effects were noted. **Dermal irritation NOAEL:** not established as irritation was noted at all doses tested. **Dermal irritation LOAEL:** 2.5% (50 mg/kg bw/day), based on erythema, excoriation, desquamation, exfoliation, necrosis, and yellowing of skin.	1147993
14-day dermal (range-finding)	Mouse	NOAEL and LOAEL were not established as this was a range-finding study. No dermal irritation was noted at 0.5% (7 mg/kg bw/day). No systemic toxicity was noted at 2.5% (35 mg/kg bw/day). Dermal irritation and systemic toxicity (body weight loss) were noted at 2.5% (35 mg/kg bw/day) and 5% (70 mg/kg bw/day), respectively.	1218838
9-day inhalation	Rat	NOAEL and LOAEL were not established as study was considered supplemental/non-guideline. Effects were noted at 0.23 mg/kg bw/day, the lowest dose tested, and included lacrimation, nasal discharge, salivation, periorbital/perinasal/perioral discharge, laboured breathing, dull corneas, decreased body weight gain in M, and decreased food consumption.	1218854
2-week inhalation (NTP Study)	Rat	NOAEL and LOAEL were not established as study was considered supplemental/non-guideline. No effects were noted at 0.198 mg/kg bw/day. Effects noted at 0.56 mg/kg bw/day included hyperplasia and squamous metaplasia of the nasal passages and turbinates.	1158499
13-week inhalation	Rat	**NOAEL:** 0.024 mg/kg bw/day **LOAEL:** 0.57 mg/kg bw/day, based on perinasal discharge and encrustation, and decreased body weight gain in M. Study was considered supplemental (several tissues were not collected for histological examination, several organs were not weighed) on its own but acceptable when combined with the 2-year inhalation study.	1218856 1218860

Study Type	Species	Results[a] (mg/kg/day)	Reference
13-week inhalation (NTP study)	Rat	NOAEL and LOAEL were not established as study was considered supplemental (no individual data were provided). No effects were noted at 0.152 mg/kg bw/day. Effects noted at 0.305 mg/kg bw/day included increased blood urea nitrogen and relative kidney weights in F, and respiratory tract lesions (goblet cell hyperplasia of nasoturbinates and septum in M, hyperplasia of the lateral wall in F, and squamous exfoliation of the nasal vestibule and nares).	1158499 1158492
2-week inhalation (NTP study)	Mouse	NOAEL and LOAEL were not established as study was supplemental/non-guideline. Effects were noted in F at 0.29 mg/kg bw/day, the lowest dose tested, and included decreased body weight gain.	1158499 1158492
13-week inhalation (NTP study)	Mouse	NOAEL and LOAEL were not established as study was considered supplemental (no individual data were provided). Effects noted in F at 0.11 mg/kg bw/day, the lowest dose tested, included increased relative liver and lung weight and inflammation of the nasal vestibule.	1158499 1158492
2-year drinking water	Rat	**NOAEL:** not established as effects were noted at the lowest dose tested. **LOAEL:** 4/6 mg/kg bw/day in M/F, based on body pallor; pale eyes; laboured respiration, unkempt appearance, yellow cutis, and emaciated body in F; and gross lesions of the stomach in M.	1147994 1147995
2-year inhalation (NTP study)	Rat	NOAEL and LOAEL were not established as study was considered supplemental (no individual data were provided; clinical observations and body weight were recorded infrequently; food consumption, hematology, organ weights, and histopathology of certain tissues were not assessed). Effects were noted at 0.25 mg/kg bw/day, the lowest dose tested, and included non-neoplastic nasal lesions (hyperplasia and inflammation of the squamous epithelium).	1109824
2-year inhalation (NTP study)	Mouse	NOAEL and LOAEL were not established as study was considered supplemental (no individual data were provided; clinical observations and body weight were recorded infrequently; food consumption, hematology, organ weights, and histopathology of certain tissues were not assessed). Effects were noted in F at 0.11 mg/kg bw/day, the lowest dose tested, and included non-neoplastic nasal lesions (hyaline degeneration of the respiratory epithelium and turbinate necrosis).	1109824

Study Type	Species	Results[a] (mg/kg/day)	Reference
Mutligeneration reproductive toxicity - drinking water	Rat	**Parental NOAEL:** 4.3/6.7 mg/kg bw/day in M/F. **Parental LOAEL:** 19.5/28.3 mg/kg bw/day in M/F, based on decreased body weight in M of the second generation, decreased food consumption in M of the first generation, encrustation of the eyes, and dental abnormalities (overgrown and broken incisors, oral lesions, malocclusion) in F of the first generation. **Offspring NOAEL:** 19.5/28.3 mg/kg bw/day in M/F. **Offspring LOAEL:** 69.1/98.4 mg/kg bw/day in M/F, based on decreased individual pup and litter weight in both generations after weaning. **Reproductive NOAEL:** 69.1/98.4 mg/kg bw/day in M/F. **Reproductive LOAEL:** not established as no adverse effects on reproductive ability were noted.	1147997
Developmental toxicity - drinking water	Rat	**Maternal NOAEL:** 68 mg/kg bw/day. **Maternal LOAEL:** not established as no adverse effects were observed. **Developmental NOAEL:** 68 mg/kg bw/day. **Developmental LOAEL:** not established as no adverse effects were observed.	1131531
Developmental toxicity - gavage	Rabbit	**Maternal NOAEL:** 15 mg/kg bw/day. **Maternal LOAEL:** 45 mg/kg bw/day, based on mortality (5 dams), clinical signs (blood in the bedding, soft faeces, diarrhea, absence of defecation), body weight loss during treatment, decreased body weight post-dosing, decreased food consumption, decreased gravid uterine weight, decreased body weight gain corrected for gravid uterine weight, irritation of the gastrointestinal tract in decedents (diffuse reddening of the fundus, thickened walls of the fundus and pylorus due to edema, ulceration of the fundus). **Developmental NOAEL:** 15 mg/kg bw/day. **Developmental LOAEL:** 45 mg/kg bw/day, based on litters with total resorptions (9 litters; only one litter had viable fetuses), decreased fetal weight, increased postimplantation loss, and increased number of early resorptions.	1131530
Reverse gene mutation assay - two studies	*Salmonella typhimurium*	One negative and one positive.	1148031 1218909
Reverse gene mutation assay - two studies (NTP)[b]	*Salmonella typhimurium*	One equivocal and two positive.	1109824
In vitro forward gene mutation - two studies	Chinese hamster ovary cells	One positive and one equivocal.	1201048 1148022

Study Type	Species	Results[a] (mg/kg/day)	Reference
In vitro forward gene mutation (NTP)[b]	Mouse lymphoma cells	Positive.	1109824
In vitro chromosome aberrations	Chinese hamster ovary cells	Negative.	1148029
In vitro chromosome aberrations - two studies (NTP)[b]	Chinese hamster ovary cells	One negative and one positive.	1109824
In vivo chromosome aberrations	Rat bone marrow cells	Negative.	1148032
In vivo chromosome aberrations (NTP)[b]	Mouse bone marrow cells	Positive.	1109824
In vitro sister chromatid exchange - two studies	Chinese hamster ovary cells	One negative and one positive.	1201048 1148011
In vitro sister chromatic exchange (NTP)[b]	Chinese hamster ovary cells	Positive.	1109824
In vivo mammalian cytogenetics - micronucleus assay - single oral dose	Mouse	Negative.	1148030
In vivo mammalian cytogenetics - micronucleus assay - single and repeat i.p. injections (NTP)[b]	Mouse	Equivocal after single dose and negative after multiple doses.	1109824
In vivo mammalian cytogenetics - micronucleus assay - inhalation for 13 weeks (NTP)[b]	Mouse	Negative	1109824
In vitro unscheduled DNA synthesis	Rat hepatocytes	Negative	1201048
Recessive lethal assay (NTP)[b]	*Drosophila melanogaster*	Negative	1109824

Study Type	Species	Results[a] (mg/kg/day)	Reference
Metabolism	Rat	**Absorption:** Approximately 5-9% and 10-30% of the administered dose was absorbed following a single 24-hour dermal application to rats and rabbits, respectively. Plasma levels following dermal applications were 100 to 1000-fold lower than those following i.v. injection at comparable dose levels. **Excretion:** The plasma half-lives after dermal application were 39-112 and 17-99 hours for rats and rabbits, respectively. Following i.v. injection, the plasma half-lives were 9.6-12 and 14-29 hours for rats and rabbits, respectively. Longer half-lives were observed at higher doses, indicating a saturation of the elimination processes. Radioactivity was highest in expired air following i.v. administration (22-80% of the administered dose). Following dermal administration, the skin contained the highest levels of radioactivity (31-60% of the administered dose), primarily in the stratum corneum. Following i.v. administration, urinary excretion accounted for 7-17% and 10-28% of the administered dose at the low and high doses, respectively. Following dermal administration, urinary excretion accounted for 1-12% and 0.5-12% of the administered dose at the low and high doses, respectively. The carcass also contained high levels of radioactivity following both i.v. (5-12% of the administered dose) and dermal administration (1-3% and 5-36% of the administered dose in rats and rabbits, respectively). Fecal excretion accounted for a minor portion of the administered dose (<5% and <1% following i.v. and dermal administration, respectively). **Distribution / target organ(s):** Following i.v. administration, the highest concentrations of radioactivity were associated with the lung, liver, blood cells, spleen, kidney, thyroid, bone marrow. In dermally dosed rats and rabbits, tissues containing the highest levels of activity included the skin, kidney, lymph nodes, large intestine, and spleen. **Metabolism:** Major metabolites were not identified. The predominant metabolic pathway for glutaraldehyde likely involves initial oxidation to the corresponding mono or dicarboxylic acid by aldehyde dehydrogenase and then further oxidation of the acidic intermediate to carbon dioxide.	1280144

[a] Effects observed in males as well as females unless otherwise reported

[b] These studies were included in the NTP report for the 2-year inhalation toxicity studies in rats and mice and were not reviewed in full by PMRA.

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Glutaraldehyde

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	MOE	Reference
Chronic dermal	NOAEL = 3	90-day drinking water study in the dog	Vomiting, decreased water consumption, and kidney effects (increased relative weight, mineralization)	300	1142317
Chronic inhalation	NOAEL = 0.024	13-week inhalation study in the rat	Respiratory tract irritation (perinasal discharge and encrustation) and decreased body weight gain (M).	100	1218856 1218860

Table 4 Alternative Sanitizers for Animal Production Facilities and Farm Equipment

End-Use Product	PCP #	Actives	Registered Uses
Effersan Concentrated Effervescent Tablets	25087	Sodium dichloro-s-triazinetrione	• Food and Beverage Processing and Food Handling Establishments • Egg Processing Plants • Milk Handling and Processing Equipment • Sanitizing Hard, Nonporous Surfaces, Dishes, Glasses, Food Processing Equipment and Utensils, Dairy and Brewery Equipment and Utensils. • Sanitizing Agricultural and Veterinary Premises
Kay Surface Sanitizer	25703	Alkyl (40% C12, 50% C14, 10% C16) dimethyl benzyl ammonium chloride, Octyl decyl dimethyl ammonium chloride, Dioctyl dimethyl ammonium chloride, Didecyl dimethyl ammonium chloride	For sanitizing food processing equipment, dairy equipment, food utensils, dishes, silverware, glasses. For sanitizing non food-contact surfaces such as floors, walls, sink tops, countertops, refrigerated storage and display equipment and other hard non-porous surfaces.
3M Sanitizer Concentrate	24041	Didecyl dimethyl ammonium chloride, Alkyl (40% C12; 50% C14 50%; 10% C16) dimethyl benzyl ammonium chloride	• Sanitizing Food Contact and Other Surfaces

End-Use Product	PCP #	Actives	Registered Uses
Concentrated Neutral Quaternary Sanitizer	15248	Alkyl (5% C12, 60% C14, 30% C16, 5% C18) dimethyl benzyl ammonium chloride, Alkyl (68% C12, 32% C14) dimethyl ethyl benzyl ammonium chloride	• Food Processing Areas • Meat Packing Areas • Egg Sanitizing • Final Rinse (3rd Sink) or Bar Glass Sanitizing • General Sanitization of Environmental Surfaces

Table 5 Use (label) Claims Proposed by Applicant Requiring Changes or That Were Unsupported

Applicant-proposed Label Claims	Accepted Label Claims	Unsupported Label Claims and Comment
HATCHERS, SETTERS, AND CHICK PROCESSING FACILITIES 1. General sanitizing of environmental surfaces prior to introduction of eggs: Remove all animals from the area. Clean out feathers, fluff, or other debris. Thoroughly saturate all surfaces with a solution prepared by mixing the appropriate amount (see Product Dilution) of GLUTEX GQ1 Sanitizer with water. Allow to stand for at least five minutes or until completely dried. Ventilate thoroughly before reuse. 2. Treatment of air and surfaces in setters with water spray cooling: Prepare a solution by mixing the appropriate amount of GLUTEX GQ1 Sanitizer with water (see Product Dilution, above). Fog or atomize this solution into setters using appropriate equipment. Treatment of air and surfaces after the introduction of eggs in low humidity hatchers with chilled coil cooling: Fog or atomize this product using appropriate application equipment	HATCHERS, SETTERS, AND CHICK PROCESSING FACILITIES General sanitizing of environmental surfaces prior to reintroduction of eggs: 1. Remove all animals from the area. 2. Remove all filth and heavy debris from surfaces by scraping or washing (e.g. feathers, fluff, and other debris). 3. Thoroughly saturate all surfaces with a 600–1200 ppm a.i. solution of GLUTEX GQ1 Sanitizer using a mop or by spraying. 4. Allow to stand for at least 5 minutes or until completely dried. 5. Ventilate thoroughly before reuse. 6. Do not repopulate with poultry or other animals, or use equipment until treatment has been absorbed or dried.	Treatment of air and surfaces in setters with water spray cooling: Prepare a solution by mixing the appropriate amount of GLUTEX GQ1 Sanitizer with water (see Product Dilution, above). Fog or atomize this solution into setters using appropriate equipment. Treatment of air and surfaces after the introduction of eggs in low humidity hatchers with chilled coil cooling: Fog or atomize this product using appropriate application equipment

References

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

3.0 IMPACT ON HUMAN AND ANIMAL HEALTH

PMRA 875632 AQUCAR 514 Water Treatment Microbiocide acute toxicity and irritancy. Bushy Run Research Center. Study number: 47-166. Study report date: November 26, 1984. DACO 4.6.1, 4.6.2, 4.6.4, 4.6.5.

PMRA 1173771 AQUCAR 514 acute inhalation toxicity study. Bushy Run Research Center. Study number: 48-3. Study report date: March 4, 1985. DACO 4.6.3.

PMRA 1218862 Skin Penetration and Pharmacokinetics of Glutaraldehyde in Rats and Rabbits. Bushy Run Research Center. Study number: 47-197. Study report date: January 15, 1985. DACO 4.5.9.

PMRA 1158493 Anuskiewicz, C.M., Ballantyne, B., Garman, R.H., McKelvey, J.A., Tallant, M.J. (1992). Percutaneous pharmacokinetics and material balance studies with glutaraldehyde. J. Toxciol.-Cut. & Ocular Toxicol., 11(4), 341-367. DACO 4.5.9.

PMRA 1131527 Glutaraldehyde dilutions: Acute peroral toxicity studies. Bushy Run Research Center. Study number: 45-124. Study report date: May 3, 1990. DACO 4.2.1.

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4.0 IMPACT ON THE ENVIRONMENT

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5.0 VALUE

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PMRA 875642 Use of Glutaraldehyde-Based Products in Egg Sanitization for Hatching Egg Treatments; 38 pgs., Union Carbide Corporation, DACO: 10.2.3.3.

PMRA 875643 Efficacy of Sanitizer 3134 (SLN# MS 990004) as a Sanitizer in Chicken Hatcheries in the State of Mississippi; 31 pgs., Union Carbide Corporation, DACO: 10.2.3.3.

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B. ADDITIONAL INFORMATION CONSIDERED

i) Published Information

3.0 Impact on human and animal health

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Haseman, J.K., Arnold, J., Eustis, S.L. (1990). Tumor Incidences in Fischer 344 Rats: NTP Historical Data. In: Boorman, G.A., Eustis, S.L., Elwell, M.R., Montgomery, C.A., Jr, MacKenzie WF (eds). Pathology of the Fischer Rat: Reference and Atlas. Academic Press, New York, pages 555–563.

ii) List of Unpublished Information Considered

Not applicable.