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HUMAN EFFECTIVENESS AND RISK CHARACTERIZATION OF OLEORESIN CAPSICUM (OC) AND PELARGONIC ACID VANILLYLAMIDE (PAVA OR NONIVAMIDE) HAND-HELD DEVICES

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14. ABSTRACT
A Human Effectiveness and Risk Characterization (HERC) for oleoresin capsicum (OC) and pelargonic acid vanillylamide (PAVA or nonivamide) hand-held devices has been conducted in an effort organized by the Air Force Research Laboratory's (AFRL), Biobehavioral Systems Branch (RHDJ), in collaboration with the National Institute of Justice (NIJ), and the Edgewood Chemical and Biological Center (ECBC). The active ingredients in these devices are collectively termed capsaicinoids and act by peripheral sensory irritation. This HERC reflects the results from a three-workshop process with sequential workshops held for data gathering and sharing, peer consultation, and independent external review of the HERC document. OC and PAVA sprays are a diverse set of more than 300 commercially available products. Because the HERC team was not able to identify sufficient information on any one product to allow the development of a product-specific assessment of risk and effectiveness, the HERC instead evaluated three products that are believed to illustrate the range of devices commercially available.

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ABSTRACT

A Human Effectiveness and Risk Characterization (HERC) for oleoresin capsicum (OC) and pelargonic acid vanillylamide (PAVA or nonivamide) hand-held devices has been conducted in an effort organized by the Air Force Research Laboratory's (AFRL) Biobehavioral Systems Branch (RHDJ), in collaboration with the National Institute of Justice (NIJ), and the Edgewood Chemical and Biological Center (ECBC). The active ingredients in these devices are collectively termed capsaicinoids, and act by peripheral sensory irritation. This HERC reflects the results from a three-workshop process with sequential workshops held for data gathering and sharing, peer consultation, and independent external review of the HERC document. OC and PAVA sprays are a diverse set of more than 300 commercially available products. Because the HERC team was not able to identify sufficient information on any one product to allow the development of a product-specific assessment of risk and effectiveness, the HERC instead evaluated three products that are believed to illustrate the range of devices commercially available.

These three "illustrative" products are based on data taken from certain selected devices and augmented by assumptions based on the professional opinion of subject matter experts. As a result, the findings of this HERC are not based on data for any specific product and cannot be used to make product-specific conclusions. The HERC's findings, however, can be applied in a general fashion for those OC or PAVA devices with characteristics that are consistent with the assumptions made in the assessment and that are similar to one of the three "illustrative" products. In addition, this analysis provides criteria in terms of velocity and composition that provide guidance for the evaluation of specific devices. Finally, the simulation tools developed for this analysis can be used in the future to evaluate devices that have appropriate exposure data.

Due to the wide variety of products, a complete assessment was not conducted for non-capsaicinoid solids in OC, propellants, or most solvents. However, a solvent consisting of 50% ethanol:50% water was assessed as part of the illustrative assessment, and an appendix presents potential effects of common solvents and propellants.

The intended effect of these devices is incapacitation from irritant effects. In the absence of adequate data on incapacitation under field use conditions, irritation was used as a physiological surrogate. The target depends on the aerosol droplet size of the material released by the device. For large aerosol droplets, the intended effect is eye irritation and blepharospasm (involuntary closure of the eye). For small aerosol droplets, the intended effect is respiratory irritation. Key potential unintended effects that were evaluated were pressure injury to the eye from the liquid stream (large droplets), aspiration (large droplets), flammability (large droplets), bronchospasm (small droplets), and effects on the deep lung (small droplets). Numerous other potential unintended effects were evaluated, but were not further assessed. Several were of potential concern, but insufficient information was available for a full evaluation (e.g., increased blood pressure, increased intraocular pressure, reactive airway dysfunction syndrome (RADS), neurotoxicity, and developmental or reproductive effects.) Other

potential effects were not evaluated because they were of limited severity (e.g., thermoregulatory effects), or their occurrence was not supported by available data (e.g., cancer). Effects of the ethanol solvent were either less severe than those of the capsaicinoids (irritation), or had thresholds well above the doses that would be received from the illustrative devices (systemic effects).

Thresholds for affecting all (or nearly all) individuals (for intended effects) and for affecting sensitive individuals (for unintended effects) were compared with exposure estimates for the three illustrative devices: stream and cone sprays (large aerosol droplets), and fogger (small aerosol droplets). The stream and cone sprays are expected to cause blepharospasm if the spray reaches the eyes. For these devices, pressure injury to the eyes may pose a significant risk of severe eye damage. Aspiration of inert liquid for the stream or cone spray device investigated in this study was not a concern based on estimates of the volume of liquid entering the mouth, but data gaps prevent elimination of concern for this effect. The risk of flammability relates to the potential for ignition of solvents or propellants by a flame or a spark. The available data suggest that the 50% ethanol:50% water mixture used in the illustrative devices assessed in this report has the potential for being ignited.

For the fogger device, induction of intended respiratory effects would be expected within a minute or less. Very sensitive asthmatics may develop bronchoconstriction at exposures less than those that cause the intended effect in healthy individuals. These sensitive asthmatics are likely to also have lower thresholds for the intended effect than healthy individuals, but quantitative information on these relative thresholds was not available. There is also very wide variability in the response among asthmatics. Healthy individuals may be at some risk for bronchoconstriction, but the dose that causes bronchoconstriction in healthy individuals is not well defined. There may be a risk of effects on the deep lung for the fogger, and this risk will increase with foggers that have low levels of solids, but the data are not sufficient to translate this potential into a probability of an effect.

A small proportion of in-custody deaths following OC use have been associated with the OC use itself, in the presence of contributing factors, such as disease (asthma) and possibly obesity or restraint. Because this risk is multifactorial and not readily quantified, it was not included in the dose-response assessment. Furthermore, a bounding estimate approach, based on the ratio of the combined in-custody death statistics to field deployments, would suggest a very small incidence rate.

Overall, the results support the conclusion that the illustrative devices evaluated in this HERC are generally effective for their intended use. However, they may cause several unintended effects, albeit with estimated low probabilities of occurrence. The approach used in this document can be used to evaluate the effectiveness and risk of other specific devices, but variability in devices is too wide to reach a broad conclusion regarding their effectiveness and risk.

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ABBREVIATIONS & ACRONYMS

AFRL	Air Force Research Laboratory
CDS	Civil Defence Supply
COE	concept of employment
DoD	Department of Defense
Dstl	Defence Science and Technology Laboratory
EC	effective concentration
ECBC	Edgewood Chemical Biological Center
ED	effective dose
FVC	forced vital capacity
RHD	Directed Energy Bioeffects Division
RHDJ	Biobehavioral Systems Branch
RHDR	Radiofrequency Radiation Branch
HERC	Human Effectiveness and Risk Characterization
HERCM	Human Effectiveness and Risk Characterization Module
HOSDB	Home Office Scientific Development Branch
IERP	Independent External Review Panel
LC	lethal concentration
LD	lethal dose
LEL	lower explosive limit
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
NIJ	National Institute of Justice
NLW	non-lethal weapon
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRC	National Research Council
ROS	reactive oxygen species
SE1	severity effectiveness level 1
SE2	severity effectiveness level 2
SE3	severity effectiveness level 3
TERA	Toxicology Excellence for Risk Assessment
USAF	United States Air Force
USEPA	United States Environmental Protection Agency

FOREWORD

This report is produced for the National Institute of Justice (NIJ) via the U.S. Army's Edgewood Chemical and Biological Center (ECBC) via contractual agreement between GeoCenters, Inc. and Toxicology Excellence for Risk Assessment (*TERA*) and its subcontractor LINEA, Inc. This report describes a Human Effectiveness and Risk Characterization (HERC) for oleoresin capsicum (OC) and pelargonic acid vanillylamide (PAVA or nonivamide) hand-held devices. The evaluation of OC/PAVA contained in this report utilized a framework for HERC (*TERA*, 2001) developed in a previous contract with Veridian Engineering (General Dynamics) (PO P66050-DSC0142). The assessment and the characterization for OC/PAVA were reviewed by an Independent External Review Panel (IERP), AFRL/RHDJ Senior Management, the National Institute of Justice (NIJ), subject matter experts, and users in a workshop in December 2004.

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The authors are very grateful for the assistance of subject matter experts and users who provided data and insights on the health effects and applications of OC/PAVA that were described at workshops held in October 2003, May 2004, and July 2004. A special thank you goes to Mrs. Hilda Hall, AFRL/RHDR, for her generous assistance with technical editing and formatting of this report.

This HERC is dedicated to the memory of Dr. Eugene Olajos, who made many seminal contributions to the field of evaluating the effects of riot control agents, and provided substantive input to this HERC. Dr. Olajos was a well-respected colleague and a beloved friend. He died of a heart attack on September 25, 2004. He will be remembered fondly and with appreciation.

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EXECUTIVE SUMMARY

The Biobehavioral Systems Branch (AFRL/RHDJ) conducted a Human Effectiveness and Risk Characterization (HERC) for oleoresin capsicum (OC) and pelargonic acid vanillylamide (PAVA or nonivamide) hand-held devices. The active ingredients in these devices are collectively termed capsaicinoids, and act by peripheral sensory irritation. OC and PAVA sprays are a diverse set of more than 300 commercially available products. Because the HERC team was not able to identify sufficient information on any one product to allow the development of a product-specific assessment of risk and effectiveness, the HERC instead evaluated three illustrative devices (a stream spray, cone spray, and fogger) that are believed to generally represent the range of devices commercially available.

The three illustrative devices are partially based on data from three commercially available devices: Brand X Stream, Brand Y Cone, and Brand Z Fogger. The stream and cone sprays are both nonivamide (PAVA) products and the fogger is an Oleoresin Capsicum (OC) product. The devices were selected as the basis for the HERC because they have relatively large amounts of information available. However, none of the three devices have sufficient information to support a comprehensive exposure assessment. As a result, additional assumptions were made that may or may not be applicable to these specific products. Therefore, the findings of this analysis cannot be used to make device-specific findings for these products, OC and PAVA spray products, or any other specific commercial device. The assessment provides insight to risks and effectiveness of the general types of devices. In addition, the approach provides insights to characteristics of the OC spray devices that are associated with elevated risks.

Due to the wide variety of products, a complete assessment was not conducted for the non-capsaicinoid solids in OC, propellants, or most solvents. However, a solvent consisting of 50% ethanol:50% water was assessed as part of the illustrative assessment, and an appendix presents potential effects of common solvents and propellants.

This HERC presents a characterization of the likelihood of intended and unintended effects from the use of the three illustrative devices. Overall, the results indicate that the use of the devices as intended would generally be effective in inducing the desired effect of peripheral sensory irritation without presenting a significant risk of unintended severe effects. Although likely to be uncommon, severe unintended effects might occur. In some cases, key data gaps and uncertainties preclude the evaluation of effectiveness and risk. These overall conclusions regarding effectiveness and risk are consistent with the current experience with OC and PAVA devices in the field, limited empirical data (primarily on the related chemical, capsaicin, as well as some data on PAVA), as well as human effects or safety assessments developed by others. Furthermore, an additional aspect of the analysis is the comparative risk. Analyses provided by law enforcement agencies indicate that increased use of OC or PAVA may likely decrease the overall injury rate of both police officers and suspects in conflict situations when compared to alternatives in the use of force continuum.

Three workshops were conducted: data sharing, peer consultation, and independent external review. The data sharing workshop identified possible sources of relevant data to determine any insufficiencies in effectively evaluating the current Non-Lethal Weapon (NLW) system. The peer consultation workshop uncovered potential data gaps, identified additional sources of data, and obtained feedback on preliminary strategies for completing the dose-response[1] and exposure assessments. This workshop also served to review the preliminary concepts being developed for the HERC modeling effort of the OC and PAVA devices. The purpose of the final, independent external review workshop was to review the draft HERC, including (1) the effects of OC and PAVA devices, (2) the dose-response assessment for these effects, (3) the exposure assessment, and (4) the characterization of the effectiveness and risk for the OC and PAVA devices. The Independent External Review Panel (IERP) submitted comments and recommendations that were incorporated into this HERC document.

The intended effect of the device is incapacitating irritation. For devices delivering large aerosol droplets, the intended effect is eye irritation. For devices delivering small aerosol droplets, the intended effect is respiratory irritation, expressed as coughing and gasping respiration.

Seven effects (two potentially intended and five unintended) were of sufficient concern and had adequate data to include in a quantitative dose-response assessment. The effects are rated by severity/effectiveness (SE) levels. SE 1 includes the intended effect and self-limited injuries that completely resolve by themselves. SE 2 effects are more serious or extensive effects, ideally receiving medical evaluation/treatment, but still capable of healing without special intervention. SE 3 effects are potentially life-threatening effects or carry a risk of significant residual disability; they require hospitalization and/or specialist care.

Using this rating system, the intended effects were: (1) eye irritation and blepharospasm (the intended effect for devices delivering large aerosol droplet sizes, SE 1) and (2) respiratory irritation (the intended effect for devices delivering small aerosol droplet sizes, SE 1). All of the unintended effects were potentially severe. They were: (1) pressure injury to the eye from the liquid stream (SE 1-3), (2) bronchospasm (SE 1-3), (3) pulmonary effects (SE 2-3), (4) aspiration (SE 1-3), and (5) flammability (SE 1-3).

Effects of the ethanol solvent were either less severe than those of the capsaicinoids (irritation), or had thresholds well above the doses that would be received from the illustrative devices (systemic effects), and so ethanol was not evaluated quantitatively in the dose-response and exposure assessments.

[1] Dose is defined as a quantitative measure of the substances or forces released by a non-lethal weapon that reach an individual and are available to induce physiological responses; the units for dose depend on the effect evaluated.

Effects of Concern Evaluated in the HERC.

Effects	Severity & Effectiveness Level	Comments
Eye irritation and blepharospasm	1	Intended effect for devices delivering large aerosol droplet sizes
Pressure injury from liquid stream	1-3	Included in quantitative assessment based on threshold data from studies with pig eyes
Respiratory irritation	1	Intended effect for devices delivering small aerosol droplet sizes
Bronchospasm	1-3	Included in quantitative assessment based on thresholds in human clinical studies
Pulmonary effects (hemorrhage, inflammation)	2-3	Included in quantitative assessment based on thresholds in animal studies
Aspiration	1-3	Included in quantitative assessment based on human fluid aspiration thresholds
Flammability	1-3	Included in quantitative assessment based on explosive limit

Insufficient data were available for an exposure assessment on any specific device, so a number of inputs to the exposure model were based on professional judgment. The following tables summarize the data needed for an exposure assessment for any specific device, as well as the sources of data for this HERC.

Source of Data Used in Modeling Illustrative Stream and Cone Spray Devices.

Inputs	Basis for Stream Device	Basis for Cone Spray Device
Concentration of capsaicinoids	Manufacturer Data	Manufacturer Data
Concentration of solvent	Manufacturer Data	Manufacturer Data
Density of spray	Manufacturer Data	Manufacturer Data
Volume sprayed per second	Manufacturer Data	Manufacturer Data
Velocity of spray at nozzle	Professional Judgment	Professional Judgment
Spray duration	Manufacturer Data	Manufacturer Data
Angle of spray (dispersion)	Professional Judgment	Professional Judgment
Fraction of spray that hits the face	Professional Judgment	Professional Judgment
Fraction of spray that hits the eyes	Professional Judgment	Professional Judgment
Fraction of spray that hits the mouth	Professional Judgment	Professional Judgment
Distribution of droplet sizes	Professional Judgment	Professional Judgment

Source of Data Used in Modeling Illustrative Fogger Device.

Source of Data Used in Modeling Illustrative Fogger Device	
Input	**Basis**
Concentration of capsaicinoids	Manufacturer Data
Concentration of solvent	Professional Judgment
Concentration of inert solids	Manufacturer Data
Specific Chemical used as a solvent	Professional Judgment
Vapor Pressure of Solvent	Professional Judgment
Molecular Weight of Solvent	Professional Judgment
Activity coefficient of solvent in water	Professional Judgment
Spray duration	Manufacturer Data
Volume sprayed per second	Manufacturer Data
Distribution of droplet sizes	Professional Judgment

Insufficient data were available to estimate dose or concentration versus probability of effect for any endpoint. Instead, this HERC developed thresholds for effects (unintended effects) or for affecting nearly all individuals (intended effects).

The intended effect for devices delivering large aerosols is eye irritation and blepharospasm. This threshold was developed from human field experience and limited animal studies. A threshold for the concentration that is irritating to the eyes of most people could not be identified. However, based on the very low threshold for eye irritation, it is prudent to assume that any significant eye contact with capsaicinoids will be irritating. Eye effectiveness was not calculated for the fogger, because the small droplet sizes of the aerosol generated suggest negligible deposition in the eyes; any deposition that could occur could not be accounted for in the model used.

The unintended effects evaluated for these devices were eye pressure injuries and aspiration. The corresponding thresholds were developed from animal data, and general human data on “dry drowning” from aspiration of inert liquids, respectively.

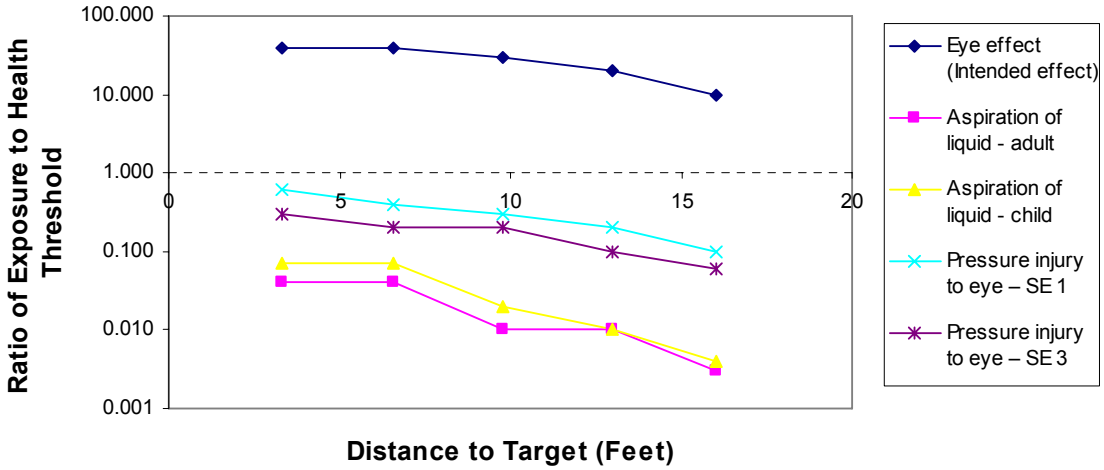
The intended effect for the devices producing small aerosol droplets is respiratory irritation and gasping respiration. Bronchoconstriction and irritation of the deep lung are potential unintended effects. Cough was used as a surrogate for respiratory irritation resulting in gasping respiration and related to incapacitation. The human clinical data on cough and bronchoconstriction from capsaicin were used to estimate thresholds for OC and PAVA. However, a number of uncertainties regarding estimates of the dose deposited to various regions of the lung limit the precision of the estimates, although these uncertainties do not appear to affect the overall conclusions.

The risk of flammability relates to the potential for ignition of solvents or propellants by a flame or a spark. The available data suggest that the 50% ethanol: 50% water mixture used in the illustrative devices assessed in this report has the potential for being ignited. A solvent was assumed to be flammable when the vapors of the solvent above the solution are capable of reaching the Lower Explosive Limit (LEL) concentration.

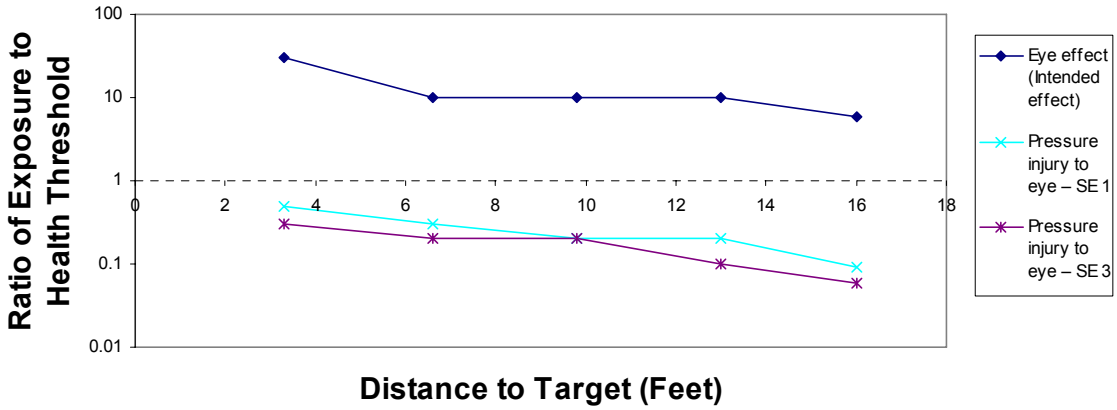
Results for the illustrative stream and cone sprays for the various endpoints evaluated are shown in the following figures. The ratios shown in these figures were calculated based on the ratio between exposure for the given scenario, and the

threshold for the effect of interest. It should be noted, however, that the threshold for the intended effect (eye irritation) is the estimated dose at which *all* normal subjects would respond, rather than a threshold at which people begin to respond. Thus, ratios greater than 1 mean that the endpoint is expected to occur (for intended effects), or has some probability of occurring (for unintended effects). These figures provide information on whether or not an effect is expected to occur, as well as information on trends with distance, but the precise value of the ratios is subject to a number of uncertainties.

Stream Spray



Cone Spray



Thus, results of this HERC indicate that both the stream and cone sprays are expected to be effective at inducing the intended irritation response in most people at all distances of intended use, if the spray reaches the eye. A small percentage of people

who are intoxicated or under the influence of drugs, described as “experiencing excited delirium,” may be resistant, but insufficient information was available to further quantitate this resistant population. Results of the analyses suggest that the illustrative OC devices evaluated do not pose a risk of eye penetration, but a number of factors raise concern for this endpoint. First, the unpredictable nature of subjects precludes the complete exclusion of the use of the devices at distances of less than 1 meter. The estimated nozzle velocity of 17 m/s for the illustrative cone and stream devices is believed to be close to the velocity associated with the SE 1 for eye damage (iris contraction). Other devices may have higher nozzle velocities, and this value may be influenced by other factors such as temperature. This endpoint is not of concern for the fogger.

For the illustrative fogger, the threshold for the intended effects (tracheobronchial irritation, based on cough as a surrogate) is the estimated dose at which *all* normal subjects would respond, rather than a threshold at which people begin to respond. Bronchoconstriction was evaluated separately for normal individuals and asthmatics. The threshold used for bronchoconstriction in healthy adults is a sub-threshold value, since there is no clear indication of what dose could cause this effect in healthy subjects. The threshold for bronchoconstriction in asthmatics varies over several orders of magnitude. The threshold for sensitive asthmatics is based on the very sensitive individuals in this spectrum. A figure comparable to that shown above is not provided for the fogger, due to the absence of an identified threshold for bronchoconstriction in healthy individuals. Based on the available data, the threshold for healthy individuals is at least 1000 times the threshold for sensitive asthmatics.

Results of the analysis for the fogger indicate that it is likely to be effective at inducing the intended irritant response within a minute or less. Very sensitive asthmatics may develop bronchoconstriction at virtually the same exposures that cause effectiveness, but there is very wide variability in the response among asthmatics, and others will experience effectiveness without bronchoconstriction. Healthy individuals may be at some risk for bronchoconstriction, but the dose that causes bronchoconstriction in healthy individuals is not known. There may be a risk of deep lung effects under the fogger scenarios; the data are not sufficient to translate this potential into a probability of an effect. Although the ratios for these effects exceed 1 for durations of 5 min and longer, there is sufficient uncertainty in the threshold that the percentage of the population that would be affected at these doses is unclear. The risk of deep lung effects will increase with foggers that have low levels of solids, but the data are not sufficient to translate this potential into a probability of an effect.

The two PAVA products which contain 50% ethanol would be considered as being potentially flammable. This finding does not indicate that all uses of the device where a source of ignition is present will result in a fire, only that the potential for the mixture to catch fire cannot be ruled out.

Numerous other potential unintended effects were evaluated, but were not further assessed. Several were of potential concern, but insufficient information was available for a full evaluation (e.g., increased blood pressure, increased intraocular pressure, reactive airway dysfunction syndrome (RADS), neurotoxicity, and developmental or reproductive effects.) Other potential effects were not evaluated because they were of limited severity (e.g., thermoregulatory effects), or their occurrence was not supported

by available data (e.g., cancer). Effects of the ethanol solvent were either less severe than those of the capsaicinoids (irritation), or had thresholds well above the doses that would be received from the illustrative devices (systemic effects).

A small proportion of in-custody deaths following OC use have been associated with the OC use itself, in the presence of contributing factors, such as disease (asthma) and possibly obesity or restraint. Because this risk is multifactorial and not readily quantified, it was not included in the dose-response assessment. Furthermore, a bounding estimate approach, based on the ratio of the combined in-custody death statistics to field deployments, would suggest a very small incidence rate.

The potential for occurrence of the various effects evaluated in this HERC can be summarized as follows:

- Eye effectiveness – expected for both the cone and stream, as long as the spray reaches the eyes; not effective for the fogger.
- Pressure injury to the eye – not a concern for the fogger; streams or cone sprays that produce droplets (greater than 26 m/s) may pose a significant risk of severe eye damage.
- Respiratory effectiveness – expected within 1 minute or less for the fogger.
- Bronchoconstriction in sensitive asthmatics - not expected for the stream or cone sprays; may occur within 1 minute or less for both fogger scenarios, but the fraction of the population where this effect will occur is not known, due to considerable variability among asthmatics.
- Bronchoconstriction in healthy individuals – not expected for the cone spray or stream; there may be some risk for bronchoconstriction in healthy individuals from foggers, but the dose that causes bronchoconstriction in healthy individuals is not known.
- Pulmonary (deep lung) effects – not expected for the cone spray or stream; there may be a risk of pulmonary effects for fogger and this risk will increase with foggers that have low levels of solids, but the data are not sufficient to translate this potential into a probability of an effect.
- Aspiration of liquid – not a concern for the fogger; not a risk based on aspiration of inert liquid for the stream or cone spray device investigated in this study. However, the lack of data on the actual amount used and the frequency of use at a distance of less than a meter prevent the elimination of concern for this effect.
- The risk of flammability depends on the solvent mixture. The available data suggest that the 50% ethanol:50% water mixture used in the hypothetical three devices assessed in this report have the potential for being ignited under certain circumstances.

Several areas require further evaluation or data collection before a conclusion can be reached regarding potential effects or risks. Key uncertainties and data gaps include:

- Comparative dose-response data for PAVA, capsaicin, and dihydrocapsaicin for key endpoints;
- Definition of effectiveness for small-droplet-size aerosols;

- Systematic statistically rigorous reporting system to measure effectiveness and adverse effects following field uses, including conditions of use, amounts of spray used, and the specific products used;
- Identification of a predictive dose metric for pressure injuries to the eye that applies to water droplets emitted from a variety of devices;
- Improved deposited dose estimates for the respiratory tract;
- Dose-response information for laryngospasm (gasping respiration from respiratory tract irritation);
- Improved understanding of the relationship between the dose-response for bronchoconstriction in asthmatics and the dose-response for effectiveness in normal subjects and asthmatics;
- Information on the impact on effectiveness in individual under the influence of drug or alcohol;
- Effects of repeated exposure, particularly on the respiratory tract;
- Improved estimate of the threshold for pulmonary effects, based on reliable dose-response data;
- Development of a self-contained pulse oxymeter that could be used on restrained people and under conditions of fogger exposure to monitor for adverse bronchoconstriction or adverse effects of laryngospasm.
- Dose-response information on neurodevelopmental effects;
- Quantitative information on tachyphylaxis (reduced response after repeated exposure);
- Quantitative information on the impact of temperature and humidity on both the dose-response of capsaicinoids, and on exposure from OC and PAVA devices;
- Additional studies on the behavior and transport of droplets formed by OC devices, including a study of the distribution and persistence of aerosols following the use of foggers;
- Information on the composition of specific products;
- Information on the potential for capsaicinoids to cause increased intraocular pressure and increased blood pressure in humans. This data could be obtained in controlled exposure studies. If such studies are conducted, it would also be of interest to collect data on hematology, clinical chemistry, and neuropsychological endpoints.
- Information on thresholds for ocular effects of solvents

Overall, the results support the conclusion that the hypothetical illustrative devices evaluated in this HERC are generally effective for their intended use. However, they may cause several unintended effects, albeit with estimated low probabilities of occurrence. The approach used in this document can be used to evaluate the effectiveness and risk of other specific devices, but variability in devices is too wide to reach a broad conclusion regarding their effectiveness and risk.

1 INTRODUCTION

1.1 THE HUMAN EFFECTIVENESS AND RISK CHARACTERIZATION PROCESS

The Biobehavioral Systems branch (RHDJ) of the Air Force Research Laboratory (AFRL) was asked to develop a risk analysis methodology to quantify the risk to human targets of a non-lethal weapon (NLW) system that takes into account the uncertainties in the models used to predict those effects. AFRL/RHDJ collaborated with Toxicology Excellence for Risk Assessment (*TERA*) to develop a framework for assessing both the effectiveness against the target and the risks of unintended effects to the target, the user, and any collateral nonbelligerent bystanders. During 2001, *TERA*, with the assistance of a panel of risk analysis experts, developed a conceptual framework to evaluate and characterize the effectiveness and risks from use of non-lethal weapons in Military Operations Other Than War (MOOTW). At that time, the panel suggested that the framework be tested with data from one or more non-lethal weapons and be subsequently re-evaluated.

Since the development of the framework (*TERA*, 2001), it has been revised and has been implemented for the evaluation of several different NLW systems (*TERA*, 2002; 2003; 2004). During this development phase, the Human Effectiveness and Risk Characterization (HERC) process was refined in collaboration with AFRL/RHDJ to include a data sharing workshop, a peer consultation, and an independent external review panel (IERP). These workshops build on each other, with the outcome being an independently peer-reviewed report. This HERC used the revised approach.

1.1.1 Data Sharing

The initial workshop in the HERC process is a data-sharing workshop. The attendees at this workshop are weapon system researchers, testing labs, users, and any additional experts that can contribute to the identification of possible sources of human effects, dose-response, exposure, or scenario data. The purpose of the workshop is to identify all possible sources of relevant data to determine any barriers in effectively evaluating the current NLW system. If there are insufficient data to begin the evaluation of the human effects, dose-response or exposure to the NLW system, then the HERC team will recommend additional research or testing. If there are sufficient data, the HERC Team proceeds to review the data and develop a detailed outline of possible human effects, as well as the relevant available dose-response and exposure data.

In October 2003, the HERC team participated in a workshop with researchers, users, and subject matter experts from the Department of Defense (DoD), National Institute of Justice (NIJ), and researchers of oleoresin capsicum (OC) and nonivamide or pelargonic acid vanillylamide (PAVA). Prior to the workshop, AFRL/RHDJ provided *TERA* with several documents on OC and PAVA, as well as primary references for some of the major human effects. At the workshop, the HERC team reviewed and discussed what data are available on OC and PAVA.

The workshop participants identified a list of potential human effects and discussed what data might be useful for assessing dose response and exposures. The participants then organized the potential effects to humans into four categories: ocular, skin, respiratory, and other effects. The effects identification (Section 3) describes specific effects identified in each of these categories. Available dose-response data for these effects were examined and discussed at the workshop, with experts identifying the most usable and appropriate data. A discussion of the dose-response data is in Section 4. For the exposure assessment, the workshop participants discussed the nature of a hypothetical target individual and how the weapon might be used (i.e., the concept of employment) to enhance the development of the HERC model. The HERC team did not conduct a comprehensive review of the refereed literature. Rather, existing review articles and tutorials were used to the extent possible. However, additional literature searches were conducted to seek further information for some effects and exposure factors, and primary references were evaluated for key data.

1.1.2 Peer Consultation

The peer consultation is the second workshop in the HERC process. The purpose of this workshop is to communicate potential data gaps, identify additional sources of data, and obtain feedback on preliminary strategies for completing the dose-response and exposure assessments. This workshop also serves to review the preliminary concepts developed for the OC/PAVA modeling effort. Feedback from the participants helps to refine the focus of the HERC.

In July 2004, the HERC team participated in a peer consultation with subject matter experts, researchers, users, and program managers from the DoD, NIJ and OC/PAVA manufacturers.

1.2 PURPOSE OF THE REPORT

The National Institute of Justice (NIJ) contracted with AFRL/RHDJ and AFRL/RHDR, who teamed in agreement with ECBC, through GeoCenters, Inc., to task TERA and LINEA Inc. to develop a HERC for incapacitant sprays formulated with OC and PAVA. This report discusses OC sprays and PAVA sprays in a general way, with the modeling focused on a generalized OC spray and two specific PAVA products. This report presents the results of this human effectiveness and risk characterization effort.

The NLW HERC framework provides decision-makers with a process for identifying the types of data needed and for organizing these data to support conclusions regarding effectiveness and risk from use of a particular NLW. To facilitate this, the NLW Risk Characterization framework utilizes the National Academy of Sciences (NAS) steps of hazard (effects) identification, dose-response assessment, exposure assessment, and risk characterization. By following these steps, an evaluation of the necessary information assists in making decisions at several levels, including weapons development and deployment.

This report is organized into the four risk assessment steps: effects identification, dose-response assessment, exposure assessment, and risk characterization. This

report does not provide extensive general discussions about the current NLW HERC framework. Instead, this report focuses on presenting information on a weapon delivery system and the results. Appendix A contains a brief description of the HERC framework (*TERA*, 2001) and some definitions of terms used in this report.

The weapon systems that have been historically examined under the HERC process have tended to be a single device, a set of similar well-defined devices, or a prototype of a device under development. In contrast, OC and PAVA sprays are a diverse set of more that 300 commercially available products (Conrad, 2004). The products are highly variable and differ in the nature of the aerosol produced, the product sprayed, and the concept of employment. During the development of the assessment, the HERC team was not able to identify sufficient information on any one product to allow the development of a product-specific assessment of risk and effectiveness.

Given this diversity and lack of product specific data, the approach used in the HERC has been to evaluate three products that are believed to illustrate the range of devices commercially available. These three "illustrative" products are based on data taken from certain selected devices and augmented by assumptions based on the professional opinion of subject matter experts. As a result, the findings of this HERC are not based on data for any specific product and can not be used to make product-specific findings. The HERC's findings, however, can be applied in a general fashion for those OC or PAVA devices with characteristics that are consistent with the assumptions made in the assessment and that are similar to one of the three "illustrative" products. In addition, this analysis provides criteria in terms of velocity and composition that provide guidance for the evaluation of specific devices. Finally, the simulation tools developed for this analysis can be used in the future to evaluate devices that have appropriate exposure data.

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2 WEAPON DESCRIPTION

2.1 RIOT CONTROL AGENTS – OC & PAVA

Riot control agents are intended to temporarily disable a targeted individual by irritating the skin, eyes, and/or mucus membranes. These agents are generally regarded as having low toxicity, but at high doses may have adverse physiological effects. The riot control agents being assessed in this Human Effectiveness and Risk Characterization (HERC) report are devices that contain either oleoresin capsicum (OC) or the "synthetic" compound, pelargonic acid vanillylamide (PAVA).

OC weapons have diverse chemical compositions, delivering a complex and variable product. There are a large number of OC aerosol devices commercially available - a recent survey identified 359 such devices (Conrad, 2004). The devices are highly variable and differ in the nature of the aerosol produced and the product sprayed.

The devices can be divided into several general categories. First, the devices can be divided into devices intended to control crowds[2] and those intended to control individuals. This assessment is limited to the devices designed to control individuals either in a crowd or in a one-on-one interaction. Second, the devices can be divided based on the form of the carrier material. These materials can include solids, foams, or liquids. This assessment is limited to those devices that use liquid carriers; devices delivering powdered OC are not addressed. The devices that use liquids and are intended to control individuals can be divided into three spray pattern categories: stream, cone, and fog. The three categories differ in the size of the droplets produced and the spread of the spray, the presence or absence of a carrier gas, and the velocity of the droplets emitted.

2.1.1 Oleoresin Capsicum (OC)

Oleoresin capsicum (OC) is an oily liquid resulting from the solvent extraction of dried ripe fruit of chili peppers. OC is a mixture of many compounds. The exact composition of OC depends on such factors as the variety of pepper used, maturity of the fruit, extraction technique used, farming conditions, and geographic harvesting location.

Because OC is derived from chili peppers, OC based devices are often termed "pepper sprays." However, the term "pepper spray" has been erroneously used by a few individuals in referring to hand-held liquid projection devices containing other and chemically different sensory irritants. In this report, the term "pepper spray" is used only when used by the author of the original reference. Because it often was not clear whether the authors included devices that also included other irritant chemicals, the term was retained, but used in quotes. Sprays based on irritants other than OC are not otherwise addressed in this assessment. The only exception was for certain effects observed with other peripheral sensory irritants (e.g., increased intraocular pressure),

[2] Products that control crowds include large area foggers, large sprays, and at the highest end additives to water cannons. These products have significantly different potentials for exposure from products that control individuals.

where these data were used to extrapolate to OC, in the absence of data on these specific effects following exposure to capsaicinoids.

The components of oleoresin capsicum that cause irritation are the capsaicinoids. This group of chemicals comprises at least six compounds. Capsaicin is the major component of oleoresin capsicum responsible for the mixture's irritant properties. Other capsaicinoids include the structural analogs to capsaicin: dihydrocapsaicin (8-methyl-*N*-vanillylnonanamide), nordihydrocapsaicin (7-methyl-N-vanillyloctamide), homocapsaicin (trans-9-methyl-N-vanillyl-7-decenamide), homodihydrocapsaicin (9-methyl-N-vanillyl decamide), and pelargonic acid vanillylamide (nonivamide) (Katz & Salem, 2004). The chemical structures for some of the capsaicinoid analogues and octanoyl-vanillamide (internal standards) are shown in Figure 1. The capsaicin used in most studies is not "ultra-pure capsaicin," and some analyses of the capsaicinoid content of even high-grade capsaicin have been shown to be a mixture of capsaicin and dihydrocapsaicin (Pershing et al., 2004). Depending on the variety of chili pepper, OC has been reported as containing from 0.01 to 0.1 % capsaicinoids on a dry mass basis (Katz & Salem, 2004). However, a recent systematic survey of OC devices reported capsaicinoid content as high as 3% (Conrad, 2004). Note that these percentages of capsaicinoids are different from the %OC reported for specific devices, which refer to the relative volume of the OC extract compared to the volume of the solvent and other components in the spray. Due to this difference between capsaicinoid content and percentage of OC in the spray, a higher percentage of OC does not necessarily mean a "hotter" and more potent spray. In this HERC, the capsaicinoids are defined as the total amount of the related compounds and no attempt is made to identify any of the individual compounds.

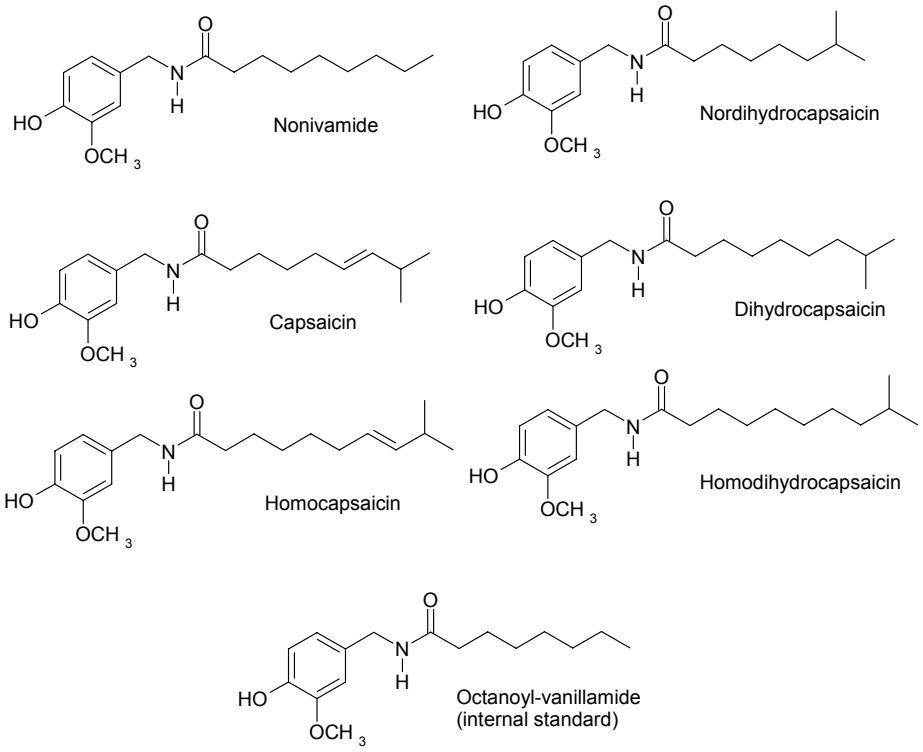


Figure 1. Chemical Structure for Capsaicinoid Analogues and Octanoyl-vanillamide (internal standard) (Reilly et al., 2001).

It has been shown that the non-capsaicinoid fraction of OC mixtures consists of more than 100 compounds. These additional compounds are carried through to the OC-based devices. The composition of these "other solids" is highly variable because there are no standards or regulations that specify OC composition (Conrad, 2004). In this HERC, these compounds are described in terms of a "total other" material, although not all devices will contain this "other" material. Due to the highly variable nature of this "other" material, it was not evaluated in this HERC.

2.1.2 Pelargonic Acid Vanillylamide (PAVA)

Pelargonic acid vanillylamide or PAVA (also known as nonivamide or capsaicin II) is a capsaicinoid that occurs as a minor (0.25%) component in certain varieties of pepper (*Capsicum annuum*) (Constant & Cordell, 1996). Because the major source of PAVA is from synthesis, rather than natural devices, it is often referred to as synthetic capsaicin. Furthermore, since it is a synthetically produced substance and not dependent on plant extraction, its strength and composition are consistent.

2.2 DEVICES EVALUATED IN THE HERC

For this HERC, a single composition for the mixtures used in OC-based devices cannot be specified. The mixtures that are sprayed from commercially available OC

weapons vary greatly across different devices. Table 1 provides the composition of several devices, as the total capsaicinoids and the percent by volume of the various capsaicinoids that comprise the total capsaicinoid content. The devices generally consist of a mixture of solvents, water, one or more of the capsaicinoids, and the other solids, as discussed above. Manufacturers define their devices in a number of ways, including the total amount of OC, the total amount of capsaicinoids, or the Scoville Heat Units (SHU)[3]. In many instances, the composition of the mixture sprays is considered confidential, and may not be known precisely, even by the manufacturer.

[3] The Scoville Heat Unit (SHU) is an accepted subjective approach for rating the apparent physiological sensation of heat generation by the mixture on mucosal surfaces (principally of the tongue). The technique involves the sequential application of progressively more dilute solutions to the tongue of human volunteer "taste tasters" until a concentration is reached at which all (or the majority) of the subjects can no longer detect a sensation of local heat. The concentration-effect relationship allows the calculation of an EC50 (effective concentration 50%), a TC50 (threshold concentration 50%) and a slope of the regression line of the effect, and the determination of a measured no-effect concentration. The SHU rating is determined by the final dilution. Pure capsaicin rates at 16 million SHU, and nothing can rate higher.

Table 1. Composition of Mixtures in Selected OC Devices.

Product	Total Capsaicinoids µg/µL	Percent Composition of Total Capsaicinoids		
		Capsaicin (%)	Dihydro-capsaicin (%)	Nonivamide (%)
The Guardian	41	49.4	48.2	2.4
Chem Armor (3.3%)	31	ND	ND	100
911 Pepper Spray (10% OC)	14	56.9	40.9	1.8
Punch II M-3 (5% OC)	5	48.9	48.6	2.5
Security Plus (Max. Strength)	2.1	48.6	47.6	2.4

(Crouch et al., 2003) ND – not determined

Potential physiological effects of OC sprays may arise due to the action of any of its possible components: the capsaicinoids, the solvent, the propellant, and the "other" materials. Because of the complex nature of the components and the lack of mandatory specifications for the mixtures used in OC devices, it is not possible to identify a single representative mixture.

2.3 Solvents and Propellants of OC Sprays

The solvents and propellants used in the manufacture of OC sprays vary from one device to another. In addition, combinations of solvents have been used in certain devices. Finally, many devices do not describe the exact solvent used or the percentage of solvent and water in the product. This use of different solvents by the different manufacturers adds to the high variability of the composition of OC sprays. Solvents identified to date are: ethanol, sec-butanol, dipropylene glycol methyl ether, d-limonene, propylene glycol, isopropyl alcohol, tetrachloroethylene, dichloromethane, and trichloroethylene (Conrad, 2004). In this HERC, the exposure assessment did not model solvent exposure, although it did calculate the flammability of the solvents, and evaporation of solvent was considered in the modeling of aerosol droplet size for the illustrative assessment of the fogger. Due to the complexity of conducting an analysis of the wide variety of solvents used, a short summary of the potential effects of the solvents used for OC and PAVA devices is presented in Appendix B.

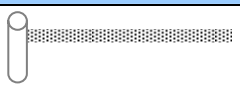
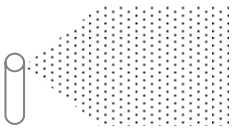
A variety of propellants is also used in the various OC sprays. Some of the propellants used are nitrogen, carbon dioxide, butane/propane mixture, and HFC134a (Dymel®). The most common propellants used are nitrogen, HFC134a, or a mixture of the two (Conrad, 2004). Due to the variability of the manufactured canister nozzles and the different propellants used, the stream pressure can vary from product to product. In this HERC, the stream pressure was modeled based on the velocity of the droplet when it reaches the eye (which depends, in turn, on the velocity at the nozzle). Pressure effects of the liquid stream to the eye are considered in the effects identification and

dose-response assessment, and a short summary of the effects of the propellants themselves are addressed in Appendix B.

2.4 SPRAY PATTERNS

OC sprays are aerosols generated though nozzle technologies that deliver the compound in a variety of spray patterns. There are three general types of spray patterns: stream, cone, and fogger. Table 2 gives the basic characteristics of the three spray patterns.

Table 2. Comparative Spray Pattern Characteristics.

Spray Pattern	Range	Accuracy	Cross Contamination	Target	Diagram
Stream	Longest	Required	Not a concern	Individual(s)	
Cone	Slightly less than Stream	Little required	Moderate concern	Individual(s) up to a small crowd	
Fog	Shorter Range	None required	Moderate concern	Crowds or clearing a space	

(Conrad, 2004)

Each spray pattern has unique characteristics as noted in the table above. The stream sprays typically have longer ranges, up to 15 ft, but require a significant degree of accuracy to hit the target individual. Stream sprays are intended for use on an individual, resulting in less cross-contamination of bystanders or users. Stream sprays are most resistant to wind than the other spray patterns. For stream sprays there are additional potential effects of concern not encountered for other spray patterns: ocular pressure injuries resulting from a direct stream hit to the eye (an effect that may also be of concern for cone sprays), and the risk of aspiration of liquid if the stream directly enters the mouth and is aspirated into the lungs.

The cone sprays emit a broad spray and disperses them over a wider area. For the PAVA cone spray evaluated in this assessment, the droplets are only slightly smaller than the stream, and so have generally similar deposition patterns. In contrast, users described OC cone sprays that were much finer droplets. Thus, the cone describes the dispersal pattern of the spray, not necessarily the droplet size. The cone pattern can cover a specific individual or more than one individual. The specific cone spray modeled in the assessment has a shorter range than the stream, but this difference depends on the propellant system, and cone sprays are not necessarily shorter range. The cone spray also requires a greater amount of spray, but requires less accuracy than stream sprays. Depending on the force of the propellant and the aerosol particle size, the broad sprays also result in an increased chance of exposure of

bystanders or users. Cone sprays using smaller droplet sizes would have decreased effectiveness in the presence of wind, and some users described a general practice of not using OC cone sprays on windy days. Smaller droplets would also increase the potential for deeper deposition of inhaled droplets in the respiratory tract.

The fog pattern is very similar to the cone spray, but has smaller aerosol particle sizes and is generally used for clearing a space or dispersing a crowd, rather than incapacitating a single individual. However, users in corrections facilities described using foggers to incapacitate individuals in enclosed spaces. A fog creates a cloud of fine droplets that will cover a larger area. The fog, similarly to the cone, has a shorter range of use and is not recommend in an environment where wind is a problem. Due to the fine droplets in the fogger, deep lung deposition also increases concern for potential respiratory tract effects. As described in Sections 5 and 6, the use of a fogger in an enclosed space creates the potential for adverse health effects resulting from exposure of the respiratory tract to potent irritants. Fogger-use scenarios may also result in more prolonged exposures than other use scenarios.

All three types of devices can create an environment that may cause secondary transfer of the active ingredient (i.e., OC) to personnel other than the intended target. Exposure from secondary transfer may cause health effects similar to those seen with direct contact (Section 3). This document does not address foreseeable possible misuse, such as accidentally spraying oneself. Devices can be designed to minimize the risk of such accidents.

The HERC investigates examples of each of the three types of devices. The two PAVA devices are examples of the stream and the cone sprays. For this HERC, a generic mixture based on what is reported to be in the Brand Z Fogger (OC product) is investigated in the fogger. This mixture is described as follows:

%OC: 10
SHU (millions): 0.5
Total Capsaicinoids: 0.33 %
Solvents/other chemicals: alcohol base

PAVA is a chemical incapacitant spray typically composed of 0.3% pelargonic acid vanillylamide (PAVA) in a 50% ethanol: 50% water mix. This mixture is used in the devices that illustrate the stream and cone spray devices.

It is important to note that while these three categories of devices can be separately described, the actual devices fall on a continuum across the three types. Variation in pressure, viscosity, and design of nozzle produce a continuum of spray types. In addition, no data on the distribution of aerosol particle sizes under conditions of use were identified for any of these devices. This means that this HERC can only be considered an “illustrative” assessment, rather than a true HERC for a specific device.

Because of this limitation, this assessment developed approaches that allow the evaluation of the impact of aerosols with differing aerosol particle sizes on the dose to the face, eyes, and respiratory tract. This approach also increases the flexibility in applying the results to other spray nozzle technologies.

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3 EFFECTS IDENTIFICATION

Most of the detailed physiological effects data for OC, its active ingredients (e.g., capsaicin, dihydrocapsaicin), and for PAVA (collectively termed capsaicinoids) have been developed to evaluate the pharmacology of these compounds on pain receptor stimulation. As a result, numerous studies have evaluated effective doses and concentrations, mechanisms, and temporal responses related to nociception (perception by nerves of injurious influences). Many other studies have evaluated the induction of reflex responses that may incapacitate, such as skin pain, blepharospasm (eyes forced shut) and lacrimation (tear induction in the eyes) associated with eye contact, as well as coughing and shortness of breath due to respiratory tract exposure.

These effects are typical of those seen following exposure to peripheral sensory irritants, a term that describes capsaicinoids, as well as several other riot control agents [e.g., 1-chloroacetophenone (CN), 2-chlorobenzylidene malononitrile (CS), and dibenz (b.f)-1, 4-oxazepine (CR)]. This class of materials causes their effects by interacting with sensory nerve receptors in skin and mucosal surfaces. A similar constellation of effects results from exposure to each of these sensory irritants, including pain at the site of contact, as well as secondary local and systemic effects such as excess nasal and tracheobronchial secretions, sneezing and coughing, and changes in breathing rate, intraocular pressure, blood pressure, and heart rate (Ballantyne, 1999, 2005; Ballantyne & Salem, 2004). Note that this spectrum of effects is distinct from direct, or inflammatory irritation. Some peripheral sensory irritants, such as CS, are both sensory and inflammatory irritants.

In addition to these acute irritation and pain responses, this assessment evaluated the potential for capsaicinoids to induce a variety of other effects that may be important for assessing physiological effects on users, bystanders, and targets. Much of the existing data have been summarized in recent reviews (Busker & van Heldon 1998; Olajos & Salem, 2001; Recer et al., 2002; Stopford & Sidell, 2004; the UK Committee on Toxicity (COT), 2004, and other reviews), and these reviews are used heavily here to identify potential physiological effects of concern. The reviews are supplemented with new studies or original literature of particular interest in identifying effects to carry through to the dose-response assessment.

As noted in Section 1, of the many possible solvents for OC and PAVA devices, only ethanol is addressed in detail in this HERC. Ethanol is highlighted because it is the solvent for the PAVA device, for which an illustrative assessment is presented here. Relevant properties of other solvents are summarized in Appendix B. The physiological effects of ethanol are well understood, particularly in the context of ingestion of alcoholic drinks. The information presented here is derived primarily from a number of recent reviews (ACGIH, 2001; Fleming et al., 2001; Grant, 1986; HSDB, 2005; IARC, 1998). The focus of this section is on effects that would be most relevant to the use of ethanol as a solvent in the PAVA spray. Since the literature on ethanol toxicology and pharmacology is very large, the relevance of effects for further evaluation in this HERC was judged based on comparisons to general considerations on the route, duration, and magnitude of potential exposures under evaluation for this HERC.

As described by the UK Committee on Toxicity (COT) (2002), a 1-second burst from a 50 mL canister of PAVA spray (as would be used in moving air) releases 8.3 g of

spray, of which 50% is ethanol. This corresponds to a release of 4.2 g of ethanol. The amount of ethanol released can be compared with the amount ingested by light drinkers. The definition of a standard drink varies by country (ICAP, 1998). In the U.S., a standard drink provides 14 g of absolute ethanol, and corresponds to 1 glass of wine (5 oz), 1 glass of beer (12 oz), or a shot of spirits (1.5 oz). Therefore, for comparison purposes, even making a worst-case assumption that all of the spray from a PAVA spray hits the body and is absorbed, this dose of 4.2 g is less than 1/3 the dose from a "standard drink" in the U.S (and half the dose from a standard drink in the U.K.), and so would not likely cause systemic acute effects, or chronic effects after repeated exposure. A direct comparison between ethanol exposure from a spray and ethanol ingestion is not possible, due to first-pass metabolism of ingested ethanol that would decrease the systemic dose following ingestion. However, the amount absorbed via the other routes would be low, as noted in the next paragraph. The actual systemic exposure to ethanol from a 1-second spray with PAVA would be much less than this worst-case, due to the lower absorption, as well as exposure scenario considerations (as described in Section 5). Much of the available data on effects of ethanol is presented in terms of blood levels, rather than ingested (or inhaled) dose, since blood levels are a measure of dose that is more closely tied to effects.

The HERC intends to be comprehensive based on the attempt to evaluate all potentially relevant physiological effects of OC and PAVA and a typical solvent, even those that would appear to be only remotely possible. The evaluation process includes effects (intended and unintended) caused by the capsaicinoids, potential for aspiration injuries, pressure injury to the eye, and a limited evaluation of secondary effects due to interaction between OC and later use of a device that could serve as a source of ignition. Due to the widely varying and uncharacterized nature of the other compounds in the OC extract, the effects of these other compounds are not characterized, except to the extent that they are identified in comparisons of OC as a whole to capsaicin or PAVA. Similarly, a complete evaluation of the effects of solvents was beyond the scope of this assessment.

In the HERC process, effects are categorized according to a qualitative severity/effectiveness (SE) scale based on the following three categories. These categories were chosen to facilitate a consistent approach for evaluating different types of effects from different non-lethal weapons technologies.

SE 1 - Self-limited injury that will completely resolve by itself.

SE 2 - More persistent, serious or extensive effects, ideally receiving medical evaluation/treatment, but still capable of healing without special intervention.

SE 3 - Potentially life-threatening effect or risk of significant residual disability. Needs hospitalization and/or specialist care.

3.1 General Mechanisms of Peripheral Sensory Irritation and approaches for evaluating Peripheral Sensory Irritants

The distinction between the generalized term “irritation” and sensory irritation is not well represented in the literature. As defined by U.S. EPA (1994), sensory irritants are chemicals that stimulate the trigeminal nerve endings in the cornea and nasal mucosa and evoke a stinging or burning sensation. In their recent review, Doty et al. (2004) stated that chemical sensory irritation refers to the broad range of physiological responses produced by airborne chemical stimulation of unspecialized free endings of the trigeminal, glossopharyngeal and vagus cranial nerves.

Peripheral sensory irritants interact reversibly with sensory nerve receptors in skin and mucosal surfaces, producing transient discomforting or painful sensations at the sites of contact, together with related local and systemic reflexes. The local reflexes result from afferent nerve stimulation in the area of peripheral sensory irritation contamination. The most relevant local reflexes for riot control agents occur at the point of contact. These are excess lacrimation and blepharospasm from stimulation of ocular (corneal) receptors and vasodilation (axon-reflex) for skin contact. Respiratory exposure results in excess nasal and tracheobronchial secretions, sneezing, cough, and changes in breathing pattern (Ballantyne, 1999, 2005; Ballantyne & Salem, 2004). The excess lacrimation and blepharospasm results in a temporary inability to see, and this transient visual impairment interferes with the ability to undertake coordinated tasks. The pain and discomfort, coupled with the reflex responses, cause harassment, a desire to vacate the area, and also hinder the performance of coordinated tasks; this forms the basis for the use of peripheral sensory irritations in the control of riots and civil disturbances, and their use in one-on-one personal protection devices. Hence the alterative name of short-term incapacitants for this group of substances.

The time to onset of peripheral sensory irritation effects is usually within a few seconds and, depending on the nature of response, they persist and subside within about 5 to 60 min. The major determinant for the occurrence of a peripheral sensory irritation response and its severity is the number of peripheral sensory irritation molecules per unit area in the region of sensory nerve receptors, and thus this is clearly related to the concentration of peripheral sensory irritation (weight/weight or weight/volume) to which the tissue is exposed. For any given individual there is a limiting (threshold) concentration for the development of a peripheral sensory irritation response, with sensation being the first indication of the development of a response. At concentrations below the threshold value there is no effect. Above the threshold there is a progressive graded response with the severity of the irritant response increasing to a maximum with increasing concentration of peripheral sensory irritation. The time to onset (latency) of the response, which is a function of accessibility of the receptors to the peripheral sensory irritation molecules, also decreases with increasing concentration. Thus, in discussions on the quantitative determinants of the presence or absence of a peripheral sensory irritation response and its severity, the major factor is the concentration of peripheral sensory irritation in contact with the tissue, such as the concentration in the medium to which the responding tissue is exposed (e.g., mg/m^3 for

inhaled materials, and mg/dL or percent or molarity for solutions), or mass of active ingredient applied per unit area of skin or epithelial surface (e.g., mg/cm^2).

Thus, the concentration of exposure to peripheral sensory irritations is the major determinant of the proportion of a population responding, latency to response, duration of effect, and potency of effect. While the proportion of a population responding to a given peripheral sensory irritation concentration may increase with the duration of exposure, this is a reflection mainly of latency to response. Exposure time is a secondary consideration in the peripheral sensory irritation response, although also a contributing factor, particularly at early time points. Also, dose in terms of total mass (mg) or mass normalized to body weight (e.g., mg/kg) is meaningless for considerations of effectiveness that depend on physiological effects related to sensory irritation or reflex responses**.** This latter dose metric is of little meaning because it refers to overall body mass, rather than to limited specific areas responding to peripheral sensory irritation materials. Similarly, the concept of cumulative dose (concentration x time) to quantitate a peripheral sensory irritation response can be misleading.

Other factors that determine the potency and latency of a peripheral sensory irritation response, at a given exposure concentration, are as follows:

(i) Particle size, as discussed in detail in Section 5.

(ii) Vehicle. With solutions of peripheral sensory irritations, the use of surface-active substances or solvents may enhance the spread or penetration of skin and mucosae, and hence facilitate the irritant response.

(iii) Environmental conditions such as elevated temperature and increased humidity may decrease tolerance to peripheral sensory irritations and hence apparently facilitate the response.

(iv) Motivation. Increased motivation and distracting influences will in general increase tolerance to supra-threshold concentrations of peripheral sensory irritation.

Normal biological variation in the peripheral sensory irritation response is seen in human populations, resulting in a typical sigmoidal exposure concentration-response curve. This distribution indicates that, for a given sensory end point, the majority of a population will respond over a limited concentration range, but implies the existence within that population of individuals who are more and less sensitive. Such variability in response to a riot control peripheral sensory irritation is clearly of importance in decisions on the effectiveness and use of a given peripheral sensory irritation for temporary incapacitation. From such frequency distribution data, it is possible to calculate median effective concentrations (EC_{50} values) for responses of different populations to a given peripheral sensory irritation, or for different peripheral sensory irritation materials in a given population (Ballantyne, 1999; Ballantyne, 2005). For just detectable (threshold) sensation plotted as a function of exposure concentration, one can obtain the 50% response (TC_{50}) in the population studied. This can also be done for more severe (incapacitating) responses. The absolute potency of different peripheral sensory irritation materials may be compared by examining the ratio of threshold or incapacitating concentrations. Unfortunately, insufficient data were available to calculate a reliable EC_{50} or TC_{50} for any of the endpoints of interest for the capsaicinoids.

When potential for toxicity and adverse human health effects are being assessed in relation to the use of peripheral sensory irritation materials, several factors need to be taken into account. First, although the major determinant for the development and severity of a peripheral sensory irritation response is the concentration of the peripheral sensory irritation coming into contact with target surface (skin or mucosa), other dose metrics may be relevant for determining toxicity. This may take into account the exposure duration, exposure dose, absorbed dose, or target tissue dose (expressed as amount of material), and/or dose normalized to body weight. (See definitions in Appendix A.)

3.2 MECHANISM OF PHYSIOLOGICAL EFFECTS FOR CAPSAICINOIDS

Although well known as peripheral sensory irritant materials, no single mechanism of action can account entirely for the varied physiological and toxicological effects of capsaicinoids. Studies on the mechanisms and modes of action of capsaicin and its analogs have been the subject of many publications (Lembeck, 1983; Marsh et al., 1987; Wood et al, 1988; Bevan & Szolcsanyi, 1990; Winter et al., 1990); these data are described in further detail in Appendix C. One of the initial issues to be addressed was whether a single mechanism of neurotoxicity can account for the capsaicin-induced neuronal degeneration. The widely accepted view is that the specific action of capsaicin on a subpopulation of afferent neurons involves the activation of a specific "vanilloid" receptor (Szallasi & Blumberg, 1990a, 1990b, 1992; Szallasi et al., 1991). The activation of the "vanilloid" receptor leads to the opening of a particular type of receptor-operated cation channel (Marsh et al., 1987; Wood et al., 1988). Sodium and calcium ion influx leads to depolarization, which triggers local release of neuropeptides (substance P, calcitonin gene-related peptide [CGRP], and neurokinin A) from sensory nerves; central protective reflexes and autonomic motor responses are also triggered (Lundblad & Lundberg, 1984; Martling et al., 1987; Stjarne, 1991). Of these neurotransmitters, substance P is most thoroughly studied. It is postulated to have a neurotransmitter role in primary sensory neurons for central transmission of afferent (incoming) information (Otsuka & Konishi, 1983) and as a peripheral mediator of neurogenic inflammation and smooth muscle contraction (Lembeck & Holzer, 1979; Lembeck & Gamse, 1982). According to Jancso et al. (1984), the influx of sodium and calcium from the activation of the "vanilloid receptor" also leads to rapid cellular damage and eventual cell death by osmosis and calcium-dependent proteases.

Release of various neuropeptides by capsaicin produces the well-studied skin pain and vasodilatation responses (reviewed in Olajos & Salem, 2001). Repeated exposures to capsaicinoids can result in decreased responsiveness to stimulation, a condition known as tachyphylaxis. This can be manifest both as a decreased response to capsaicinoids (desensitization), and as a decreased response to any stimulus (neuroinhibition). This latter effect is exploited by capsaicinoid treatments for chronic rhinitis (runny nose) or skin pain. The release of neuropeptides also alters neurophysiology of sensory neurons in the airway mucosa, as well as neuromediated inflammation of the respiratory epithelium, of airway blood vessels, of glands, and smooth muscle. The above consequences of this response result in respiratory symptoms, including bronchoconstriction, edema of the tracheobronchial mucosa, enhanced vascular permeability, enhanced mucous secretion, and neutrophil

chemotaxis (Lundberg & Saria, 1982a, 1982b; Hua et al., 1984; Lundberg et al., 1983a, 1983b, 1984; Saria et al., 1985; Theodorsson-Norheim et al., 1985; Helme et al., 1987; Tominack & Spyker, 1987; Umeno et al., 1990; Blanc et al., 1991; McDonald, 1992).

The toxic metabolites (e.g., semiquinone and quinone derivatives, methyl radicals) of capsaicinoids and their biological interactions with cellular targets may also play important roles in inducing responses of toxicological interest (Surh & Lee, 1996). Quinone derivatives of many xenobiotics produce toxic effects *in vivo*, including cytotoxicity, carcinogenicity, and immunotoxicity via alkylation of critical cellular targets or formation of reactive oxygen species (ROS). The metabolism of capsaicinoids also produces methyl radicals as reactive intermediates. These radicals are well-known to alkylate nucleic acids and proteins. The alkylation of proteins and/or glutathione (GSH) by electrophilic metabolites of capsaicin may have consequences affecting cellular energetics, detoxification processes, or other biochemical processes. For example, capsaicinoids are capable of covalent binding and inactivation of microsomal proteins, as has been demonstrated for the cytochrome P450 enzyme CYP2E1 (Reilly et al., 2003b). This effect may account for the impact of capsaicinoids on xenobiotic metabolizing enzymes and liver toxicity. In addition, since CYP2E1 is important in metabolic activation and metabolism of many chemicals, this inhibition indicates that long-term systemic exposure to capsaicinoids can interact with other exposures.

3.3 Experience in Police and Correctional Uses

3.3.1 Effectiveness and Safety Evaluation

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In considering the human effectiveness of OC and PAVA products, subjective data from users emphasized the importance of human factors and other psychological aspects of the response. For example, several police departments reported obtaining compliance merely from the sound of the Velcro® as the officer unfastens the holder containing the OC or PAVA delivery device. In other cases, the culture of the target plays an important role. Police officers described a “street culture” that expects the target to resist physical force from police officers, but considers it acceptable to “give in” to a chemical spray. Although such phenomena are important aspects of an effectiveness and risk characterization, data were not available to quantify these effects. A systematic reporting system would be useful to further describe and quantify the impact of these factors.

Another important aspect of an effectiveness and risk characterization, particularly for devices delivering small aerosol droplet sizes, is the importance of motivation in determining effectiveness. Police officers using OC delivered as a cone spray described frequent exposure from back spray in the line of duty, and learning to “fight through” the effects. They attributed much of the effectiveness of this device to the panic response from difficulty in breathing due to the cough reflex. Presumably due to the importance of fear in determining effectiveness, effectiveness was higher in young targets, and lower in those who had been exposed repeatedly. In contrast, the blepharospasm response from the larger aerosols results in involuntary closure of the exposed eye, as well as sympathetic closure of the unexposed eye. This temporary visual incapacitation of the target markedly reduces the effectiveness of any movement by the target. In addition, personal reports from users of PAVA delivered as a stream

indicate that in some cases the pain is so severe that the target is unable to physically resist, even by general struggling. While PAVA has been described as highly effective based on interviews with users (HOSDB, 2004), in some cases the ability to fight though the effect has been described (albeit with eyes closed). The absence of an effect has also been reported where the subject was under the influence of alcohol (HOSDB, 2004). The importance of aerosol droplet size and its influence on the nature of the incapacitating effect is highlighted throughout this assessment, particularly in the discussion of respiratory effects (Section 3.5) and exposure (Section 5).

Reports in the literature on the effectiveness of OC vary, presumably at least partially due to methodological differences and differences in definition of effectiveness. Other possible differences between studies include differences in strength and composition of the product, training methods, type of spray (fog, cone, or stream), number of suspects in the study under the influence of drugs, and where the spray falls on the use of force continuum for the police force being studied. Most of the reports on effectiveness did not address physiological effects (intended or unintended) beyond the discussion of effectiveness. Where the studies did address effects, the effects are described later in this report.

Several investigators have studied the effectiveness of OC use by police agencies. Kaminski et al. (1999) reviewed the literature on effectiveness. They noted that most evaluations reported 85-100% effectiveness, but a 1997 review of 325 OC spray incidents found only 73% effectiveness. As part of an evaluation of deaths in police confrontations where OC was used, Petty (2004) stated that the overall effectiveness of OC, as reported by the officers involved in the study was 20%. However, it was not clear if this number focused on the confrontations included in the study, for which a high percentage involved drug use; the high percentage of drug use would lower the effectiveness. Petty compared his results with a survey conducted by Nowicki (1993), which determined that OC was partially, moderately, or very effective >90% of the time. The difference in results may have been due to differences in definition of effectiveness or differences in the types of confrontations evaluated. Based on a survey of the literature, Busker and van Helden (1998) concluded that “pepper spray” was successful in 85-90% of the cases used. “Success” was not defined, but appeared to mean sufficient incapacitation so that the suspect could be safely removed.

Kaminski et al. (1999) used a survey instrument to evaluate effectiveness of OC in the Baltimore County Police Department. The OC delivery system employed by this agency was a 3-ounce container of OC with a fog delivery system, rated at 2,000,000 SHU. Further details on the aerosol droplet size or brand of the OC were not provided. Misses, canister malfunctions, and use in crowd situations or on animals were excluded, leaving a total of 690 incidents. The authors noted that there was wide variability in the effectiveness, with immediate and complete incapacitation seen for some subjects, some subjects being unaffected for a short time before they are incapacitated, and others who are completely unaffected. They evaluated whether the OC eased arrest and whether the suspect was incapacitated, and used a 6-category variable to describe the suspect behavior after exposure. Together, the data on behavior and eased arrest were used to develop a 5-category variable describing the effectiveness of OC. Overall, OC eased arrest in 85.3% of the cases, and incapacitated the suspect in 70.7% of the uses. The overall percentage considered “totally effective,” “effective,” “minimally

effective," "ineffective," and "totally ineffective" was 28.2, 42.5, 14.7, 10.3, and 4.3%, respectively. Further analysis found that the effectiveness was highest in the youngest group (age 14-21 years), followed by the oldest group (38-66 years). There was a small but statistically significant decrease in effectiveness with increasing body weight. A strong significant decrease in all measures of effectiveness was seen with suspects on drugs (e.g., 47.1% incapacitated vs. 71.6% in those not on drugs, alcohol, or mentally disturbed). Alcohol ingestion did not decrease effectiveness, and all of the effectiveness measures (e.g., 73.2% incapacitated, and 70.6% eased arrest) indicated that OC was more effective on the mentally disturbed than on suspects on drugs. The authors noted that judgment of mental disturbance, drugs, and alcohol use was subjective. Finally, OC was most effective in the range of 3-4.5 ft, and was somewhat less effective at shorter or longer distances. Interestingly, 60% of uses were at less than 2.5 ft, while the distance recommended during training was 4-6 ft. Overall, this study provides a start for combining the physiological responses addressed in the remainder of this effectiveness and risk characterization with human factors. While some of the factors described by the authors affect the OC dose received, a similar survey instrument and multivariate regression analysis (either based on the raw data collected by Kaminski et al., 1999, or based on new data collected in future deployments) could be combined with the effectiveness and risk characterization to provide a more complete assessment of effectiveness, particularly for the spray delivery systems.

A NIJ report (Ashcroft et al., 2003) presented the findings of two unpublished NIJ-funded studies testing OC effectiveness and safety. One study addressed the issue of in-custody deaths, and is described in Section 3.3.2. The other study was conducted by the University of North Carolina's Injury Prevention Research Center. The purpose of the study was to evaluate the effectiveness of OC spray. This was based on evaluation of police officer injuries from assaults (excluding injuries from motor vehicle crashes and injuries unrelated to arrest), suspect injuries, and excessive force complaints. Data were collected in monthly increments for three police departments for a total of 7-9 years, including at least 2 years prior to and after the introduction of OC[4]. Statistical analyses were conducted to compare the number of reports of injuries or complaints before and after the introduction of OC, but there was no concurrent control. Only one department had sufficient data on excessive force complaints to support a statistical analysis. The results suggested a relationship between the use of OC and decline in officer injuries in one of the three departments, decline in suspect injuries in another department, and a decline in excessive use-of-force complaints in one department. OC may have contributed to decreased officer injuries in two other departments and decreased suspect injuries in a second department, but the data were not sufficient to support a statistical association.

Research was conducted by the International Association of Chiefs of Police (IACP) to evaluate the effectiveness of OC spray in police confrontations with humans and animals (Edwards et al., 1997). The OC spray used contained a 5% concentration of OC delivered through a fogger system. During the study period, OC was used in 194 incidents (174 human and 20 animals). The suspects were generally intoxicated (drugs

[4] Data collection was based on pre-existing department records or workers compensation and medical-only claims files.

or alcohol), belligerent and/or combative. Of the 174 individuals sprayed with OC, 156 were incapacitated enough to be effectively arrested. The OC spray was generally used within 3 ft of the suspect and sprayed to the suspect's face. A single short burst of spray to the face was effective in 144 of the incidents, and in only 4 incidents the canister was emptied. Seven suspects were recorded as having no incapacitating effect resulting from the OC exposure, but were reported as either exhibiting drugged behavior or appearing to have "emotional problems" (Edwards et al., 1997, p. 9) [*sic*] indicative of mental instability. This term was not further described, but may have referred to "excited delirium," further discussed in Section 3.3.3. In all 20 incidents involving animals, OC spray was 100% effective. Overall, the report showed that OC spray was effective in 85-90% of the cases and resulted in a decrease in injuries to the officers and suspects.

An early FBI study (Weaver & Jett, 1989) reported on the exposure of a number of volunteers. No side effects or adverse reactions were reported among 899 OC-exposed volunteers, but the level of post-evaluation was not available. In a group of 59 volunteers sprayed with OC solutions of 1-5% on the face, symptoms included ocular inflammation, and swelling of capillaries in eyes, nose, and throat. Pulmonary symptoms ranged from coughing to shortness of breath to bronchoconstriction. Four individuals reported short-term nausea, and 6 reported temporary loss of upper body motor skills (possibly due to hysterical paralysis), disorientation, and fear. In none of >2000 cases evaluated in this study was there damage to the eyes (method of measurement not reported, presumably means no long-term damage), skin rash, or blister formation.

Smith and Stopford (1999) briefly reviewed medical complaints of corrections officers exposed to OC spray (additional information not available) during training exercises; additional details were provided in Stopford (2004). Of approximately 6000 exposed individuals, 61 received medical care. Thus, approximately 1% of the entire group had effects sufficiently severe to result in medical care, although the incidence varied with different training groups. No control group was monitored, but the type and severity of several of the endpoints suggest that at least some of the observed effects were exposure related. The most common complaint (28 patients) was eye irritation, including conjunctivitis, keratitis, corneal abrasions, conjunctival blistering, and one individual with eye burn, resulting in 5 days' loss of work. The next most common symptoms were chest symptoms (20 patients, one with an allergic reaction and four with asthmatic reactions[5]), headache (16 patients, with 9 cases described as severe), and hypertension (11 patients). Severe hypertension (>180/110) was noted in two patients. Other severe effects were loss of consciousness (2 patients), and cardiovascular effects (electrocardiogram [EKG] change in one and chest pain requiring nitroglycerin in one). Adverse effects persisted more than one week in 13% of the trainees seeking medical attention. It is not clear why this study reported more frequent and more severe effects that were not reported by other studies. However, the authors did note that one group

[5] The study author reported that the differentiation was based on medical records, not his independent assessment. Allergic symptoms/findings among the 61 officers seeking medical care included hives (uriticaria), asthma (which may have been aggravation of a pre-existing condition, i.e., induction on non-specific airway reactivity or bronchospasm from the irritant effects of OC) and an allergic respiratory reaction, not otherwise specified (W. Stopford, personal communication, 2005).

of trainees had a much higher incidence of effects. This suggests that either a more potent batch of OC may have been used by that group, the aerosol droplet size was smaller (resulting in more respirable material), or there may have been some other difference in training procedures.

3.3.2 Deaths in Custody

3.3.2.1 OC

There have been a number of reports of in-custody deaths associated with OC or "pepper spray" use by police forces. This has raised the question of whether those deaths were causally-related to the OC or "pepper spray," to some other aspect of the confrontation, or whether the deaths were due to some factor unrelated to any action by the police. Two approaches have been used to address this issue. One is a case study approach, evaluating reports of in-custody deaths, and the second approach involved controlled clinical studies.

A NIJ report (Ashcroft et al., 2003) presented the findings of an unpublished NIJ-funded study by the University of Texas, Southwestern Medical Center, on in-custody deaths. The study reviewed 73 cases of in-custody deaths allegedly associated with the use of OC. Of these 73 cases, 10 were excluded because of insufficient detail in the case reports or because further investigation showed that OC was not used. The remaining 63 cases were separated into 4 categories: cause of death was clear and well-founded, cause of death could be attributed to two or more factors working together, outliers, and asthmatics. Only minimal information was provided on how the cases were assigned to the various categories, but the study authors stated that reports were collected from a range of sources, including police reports and information from medical examiners and toxicologists. The "clear-cut" cases included deaths attributed to drugs, heart disease, or positional asphyxia. The deaths assigned to two or more factors included deaths attributed to combinations of drugs, disease, and the confrontational situation. The authors stated that for both of these categories, "pepper spray was ruled out as a direct or contributing cause in all of these deaths" (Ashcroft et al., 2003, p. 11), but they did not provide additional details. The study concluded that OC was not a contributing factor in 61 of the 63 in-custody deaths. In the two deaths in the asthma category, the deaths were attributed to the disease, with OC use as the precipitating factor. In one case, there were signs of pre-existing asthma, and the medical examiner described the cause of death as asthma precipitated by the use of OC. In the second case, there were no signs of asthma, but the subject had airway damage that could have resulted in susceptibility to bronchospasm. In this case, OC and disease were listed as the cause of death. The study also addressed the issue of positional asphyxia, which was considered a contributing factor for in-custody deaths with or without the use of OC.

The term asphyxia refers to a restriction of breathing. Positional asphyxia is a term used to describe the placement of a body in a position that results in impaired ability to breath. Body positions that can result in positional asphyxia are also referred to as "hog-tie" and "hobble." The "hog-tie" method involves securing both wrists and ankles together behind the back, while the "hobble" method secures the hands behind the back separately from the secured ankles. Breathing can be restricted by

compression of the chest or abdomen as well as restricting or blocking the airway. Obesity or weight on the subject's back (e.g., an officer's body weight in attempting to subdue the subject) increases the risk of positional asphyxia.

Other reviews of case studies have identified common factors in the in-custody death cases, including combative or bizarre behavior, and struggles with the police. Most cases involved drugs and/or alcohol, the application of restraints after spraying, and complete or partial ineffectiveness of the OC spray. Death almost always occurred immediately or soon after the confrontation. Granfield et al. (1994) reported on 30 cases of in-custody deaths; there was sufficient data for evaluation in 22 of the cases. Evaluation of police reports and autopsy findings found that OC was not the cause of death in any of the 22 cases. In the one case where the autopsy listed OC as a factor in the death, the secondary review of the data by Granfield and colleagues did not support that conclusion. Based on their review of the cases, Granfield et al. (1994) attributed death either to positional asphyxia, with drugs or disease as contributing factors, or solely to drugs and/or disease. Death was often attributed to abnormal heart rhythm, with drugs, alcohol, and the stress of the struggle being contributing factors. Steffee et al. (1995) reported in greater depth on two cases evaluated by Granfield et al. (1994). They concluded that the first case was unrelated to OC. However, they concluded that the data in the second case suggested a direct contribution of OC to the death, with contributing factors including physical stress during the struggle, underlying pulmonary disease (bronchitis), alcohol intoxication, and physical restraint. In this latter case, a man was sprayed 10-15 times (some of which did not hit the face), there was a rapid onset of dyspnea after the spraying, and there was a complaint of breathing difficulty while seated in an upright position.

Hobbs and Rice (1997) noted that newspaper articles have reported a rise in in-custody deaths in California associated with increasing use of OC. However, no thorough analysis of this reported phenomenon and potential confounding factors was available, and the reported increase cannot be definitively associated with OC.

The second approach to evaluating the role of OC in in-custody deaths has been to conduct controlled clinical studies of the effect of the interaction of OC with positional restraint. Chan et al. (2001, 2002) conducted a randomized cross-over controlled trial evaluating the effect on respiratory function of OC alone and combined with positional restraint. The study was conducted with 34 healthy young law enforcement recruits. Of these, 7 were considered overweight, and 8 had a history of smoking, lung disease, or respiratory inhaler medication use. The subjects were exposed via inhalation only to OC (Cap-Stun as a cone spray aerosolized into a box) or a placebo, followed by 10 min either sitting or in a prone maximal restraint position. Goggles were worn to exclude eye exposure. There was no effect of OC on percent forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), oxygen, or CO_2 levels, as measured at 1.5 and 10 min after exposure. In contrast, maximal restraint decreased FVC and FEV_1, both for the placebo and OC-exposed groups, but there was no significant difference among those restrained between the OC- and placebo-exposed groups. Blood pressure, however, was increased in the groups exposed to OC (Chan et al., 2001). This increase may either have been due to direct result of the OC exposure, or as a result of stress from the pain, as discussed further in the section on cardiovascular effects. The study authors noted a number of limitations in extrapolating these results to field

conditions. Stress was minimized for the test subjects, due to the absence of a physical struggle, psychological stress or stress from eye pain. In addition, the subjects knew medical care was at hand.

In summary, a small proportion of in-custody deaths have been associated with OC use in the presence of contributing factors, such as disease (asthma) and possibly obesity or restraint. Because this risk is multifactorial and not readily quantified, it was not included in the dose-response assessment. Furthermore, a bounding estimate approach, based on the ratio of the combined in-custody death statistics to field deployments, would suggest a very small incidence rate.

3.3.2.2 PAVA

PAVA products are currently not widely used in the U.S. There have been no reports of in-custody deaths associated with use of PAVA abroad. However, the number of instances of use is much smaller, limiting the sensitivity of this result. Based on information provided by one manufacturer, there have been only approximately 3000 reports of use abroad, compared to at least tens of thousands of instances of OC use in the U.S. Therefore, the conclusion that PAVA use raises minimal concern regarding in custody deaths is based on limited data on PAVA, and on extrapolation from evaluation of OC. However, as for OC, there may be some small risk for people with underlying lung disease. Note that any differences between PAVA and OC are likely to be due to differences in the delivered aerosol droplet size, rather than chemical or toxicological differences between PAVA and the related OC mixture. As described further in Section 2, commercial OC products deliver a variety of aerosol droplet sizes, including some that deliver aerosol droplets small enough to penetrate the respiratory tract. In contrast, the commercial PAVA product evaluated for this assessment delivers aerosol droplets too large to enter the respiratory tract.

3.3.3 Excited Delirium

A particular challenge for the effective deployment of non-lethal devices appears to involve individuals under the influence of drugs or alcohol, or with mental disturbances. These individuals may be extremely aggravated, excited, violent, and unable to reason. The term “excited delirium” has been applied to this population and is described as “an acute mental disorder characterized by impaired thinking, disorientation, visual hallucinations, and illusions” (Wetli & Fishbain, 1985, p. 878). Laur (2004) discussed in-custody deaths related to restraint and excited delirium. Laur summarized a report conducted by the Ontario Coroner’s Office (1998), which studied 21 cases of in-custody deaths. Many of the deaths in the 21 cases were attributed to excited delirium and restraint. Four of the cases involved the use of OC spray, but no further details on what contributed to these deaths were given.

Use of non-lethal agents on people with excited delirium may be more challenging than use on the general population. Non-lethal agents may be less effective on people with excited delirium, which may lead to multiple applications of the non-lethal agent, increasing the exposure of the target individual. Further complicating the issue, physiological differences in these people may result in their being at increased risk for adverse effects for a given dose of non-lethal agents. People

exhibiting excited delirium may also be at increased risk from the stress of the confrontation, such as in some cases of in-custody deaths. Thus, the risk of adverse effects may be higher in this population, due to higher exposure, higher physiological susceptibility, and possible co-exposures besides the alcohol or drugs (e.g., stress) that increase susceptibility.

Although excited delirium from drug use is a general issue for use of riot control agents, including OC, Busker and van Helden (1998) noted that it has been claimed that OC is more effective on people under the influence than other irritants such as CN and CS. The reason provided was that the analgesic effects of drugs or alcohol have less of an impact on the effects of inflammatory agents. No data were provided to support this suggestion.

The available data are insufficient to quantitatively take into account the implications of drugs or alcohol (and their associated effect of excited delirium) on the effectiveness or risk from the use of OC or PAVA, but this issue is noted in the Effectiveness and Risk Characterization.

3.4 OCULAR EFFECTS

3.4.1 OC

Capsaicinoids are potent eye irritants, with exposure resulting in a rapid severe burning pain, lacrimation (watering of the eyes), redness, conjunctival inflammation, swelling, and blepharospasm (involuntary eye closing). The eyes may be forced shut by the degree of irritation. Most of the effects are self-resolving (SE 1). Depending on the aerosol droplet size of the OC spray used, the incapacitation due to eye effects may be the intended effect, and the primary source of the incapacitation.[6] The hydrophobic nature of capsaicinoids may allow them to penetrate the corneal surface into the corneal epithelium, where nerve terminals are located. This ease of penetration aids in the rapid effectiveness of capsaicinoids for incapacitation due to eye effects. Penetration can be enhanced by hydrophobic solvents. The solvent carrier can also cause corneal burns. OC spray can also be absorbed by and cause changes to soft contact lenses (Holopainen et al., 2003). This “trapping” of the spray by the contact lens could increase the duration of exposure to both OC and the solvent, thus increasing the potential for ocular injury. OC sprays may also cause disintegration or dissolution of contact lenses, although this effect is likely due to the solvent carrier, rather than the OC itself. Conversely, there have been reports with other sensory irritants (e.g., CN and CS) that the use of soft contact lenses decreased the ocular effects of these chemicals. These data are described in more detail in Appendix D. Law enforcement officers consulted in the development of this HERC noted the training recommendation that soft contact lenses be removed after OC use and discarded.

Almost no dose-response or concentration-response data are available for the irritant effects of capsaicinoids, partially due to concerns about conducting pain studies

[6] While one might expect that the eye effects would be an intended effect for all scenarios, police officers using at least one OC cone spray device reported minimal incapacitation from eye effects, and attributed the incapacitation entirely to respiratory effects. As described further in Section 5 (Exposure), this is because the small size aerosol particles have minimal deposition to the eyes, and are delivered primarily to the respiratory tract.

in humans or animals. However, Jancso et al. (1968) reported a severe pain, blepharospasm reflex, and dye leakage from blood vessels after instilling 50 μg/L (1.6 E-7 M) capsaicin into rat eyes. In the absence of data on OC, this concentration is also considered to apply as an effect level to OC. Other data suggest that the air concentration threshold for eye effects (species not identified) for OC and capsaicin is <0.012 mg/m^3 (Dubay & Rush, 1998). While additional eye irritation data were located for formulated animal repellants containing capsaicins, the studies did not provide sufficient data on the percent capsaicinoids of the repellant, or on other components. Therefore, these proprietary data cannot be used quantitatively, and are not presented here.

In a controlled clinical study of 10 officers exposed to OC, Vesaluoma et al. (2000) reported immediate changes in mechanical and chemical sensitivity that persisted for a week. Cap-Stun spray (5.5% OC, 64% isopropyl alcohol, and 30.5% isobutane propellant) was used at a distance of 1.5 - 2.5 m for 0.5 – 1.5 s. Focal epithelial damage healed within 1 day. In a study of 47 subjects exposed to OC as part of a training exercise, blepharospasm was present at 10 min, but not 1 h (Zollman et al., 2000). The subjects were sprayed at a distance of 1 meter with one of two OC products: either Deftec (0.5 million SHU) or Southern Cross Tactical Defense Spray (1 million SHU). Punctate epithelial erosions were observed in 20/94 eyes at 10 min, a response that decreased to 15 eyes at 1 h, but there were no frank corneal abrasions. Pain was markedly decreased within an hour. Corneal sensation was nearly absent at 10 min and still markedly reduced at 1 h. It has been noted that decreased mechanical sensitivity of the eye (indicative of desensitization) could lead to secondary effects, such as eye injury due to decreased ability to notice particles in the eye (DiBartolomeis et al., 1993). No cases of such effects have been reported.

There have been several reports of corneal abrasion following use of OC. While the effect was clearly attributable to the spraying incident, reports of abrasions after exposure to training sprays containing only solvent (Holopainen et al., 2003; Lee et al., 1996) show that the abrasions are not a direct result of the capsaicinoid exposure. Instead, they may be due to the solvent delivery system, several of which are irritating chemicals themselves. Corneal abrasion also appears to be enhanced by rubbing the eyes, illustrating the importance of preventing subjects from doing so after being sprayed. This effect raises a potential concern for an exposed child who may not follow such instruction. The reduced corneal sensation after spraying removes a feedback mechanism, heightening the risk corneal abrasions from rubbing of the eye. Spraying in areas with high background dust levels may also increase the risk of abrasion (Zollman et al., 2000). Corneal abrasion is considered a SE 2 effect. The effect is not due to the capsaicinoid component of the OC, and there is a large degree of variability in the carrier and other factors contributing to abrasion, so no concentration-response assessment is possible for this endpoint. However, because a natural response to eye irritation is to rub the eyes, and this response is of particular concern for exposed children, this endpoint will be addressed qualitatively in the assessment.

Holopainen et al. (2003) described four subjects who developed corneal erosion after being exposed to “pepper sprays” or related training sprays. One of these was exposed to an inert training spray containing 92% trichloroethylene and no OC. Long-lasting deep corneal and conjunctival erosion was observed in all subjects, and one

subject exposed to an unidentified Russian-manufactured spray at a distance of about 50 cm (no further details available) had sustained nerve damage to the subbasal nerves of the eye. These case reports support the conclusion that corneal abrasion and other eye effects observed in some cases may be attributable to the solvent itself.

Watson et al. (1996) conducted a retrospective evaluation of 81 people who came to the emergency room after exposure to OC (5% Cap-Stun spray) in law enforcement confrontations. Corneal abrasions were reported in 23% (7/30) of the cases where fluorescein staining was conducted. The authors noted that the cause of the abrasions was not clear, but did not appear to be related to contact lens use. Since 908 people were exposed to OC spray during law enforcement actions during the study period, and 81 were brought to the emergency room, primarily as a result of the OC exposure, rather than concurrent injuries, the authors suggested that approximately 10% of the uses of OC resulted in the need for medical treatment beyond the flushing of eyes and skin performed by officers in the field. Most of the patients presented with burning and redness of the eyes and/or burning and redness of the skin. Resolution was rapid.

Brown et al. (2000) reviewed the logs of visits to a jail ward emergency room for 100 cases of “pepper spray” use. The “pepper spray” was described as a 10% spray, with no further description. Scleral injection (bloodshot eyes) was reported in 38 patients, and 7 had corneal abrasions. The authors noted that the incidence of corneal abrasions could not be calculated, since the total number of cases of sprayings was not available. A slightly alkaline conjunctival pH of 8 was reported in 2 patients; this returned to normal after irrigation with saline.

3.4.2 PAVA

The in-use formulation of PAVA (0.3% in a 50% aqueous ethanol solution) produced eye irritation in a test conducted according to the standard OECD method (Chevarne, 1995). Significant irritation (including some evidence of opacity of the cornea and damage to the iris) was seen immediately after instillation through 3 days after exposure. All of the animals recovered within 7 days of exposure. These data indicate that PAVA is irritating to the eye, but long-term effects from the chemicals in the in-use formulation are unlikely. The EC_{50} for PAVA in a guinea pig eye blink test was 0.15 μM, or 46 μg/L (Battensby et al., 1981). This concentration is defined as the one that produces in half the tested animals an eye blink rate of at least 5 times/20 s or closed eyes for several seconds. The authors noted that this made PAVA 100 times as potent as CS for ocular irritancy in concurrent testing. However, they also noted that this assay was useful primarily as a screening assay based on a sensitive threshold endpoint, rather than as a ranking test, and that their guinea pig eye blink test data were not accurately predictive of the relative potency in humans of various riot control agents. Although no direct relationship between the EC_{50} and irritancy in humans was located, Bar-Ilan (1997) reported that a blinking index (blinks after exposure compared to blinks with normal saline) of 1.6 corresponded to a solution that elicited pain in 95% of human subjects. The control level of blinks in humans was 18.9 blinks/5 min, indicating (based on the definition of the EC_{50}) that the EC_{50} in guinea pigs of Battensby et al. (1981) was well above the blinking index of 1.6, and thus would be expected to elicit pain in >95%

of people. Another study reported that the air concentration threshold for eye effects (species not identified) for PAVA is <0.036 mg/m^3 (Dubay & Rush, 1998).

No controlled clinical studies were located for effects of PAVA on the eye. In discussions with users abroad, one described an immediate involuntary blepharospasm, with sympathetic closure of the other eye, even without exposure. Copious tearing and eye redness were also reported. PAVA is believed to be effective even on people wearing glasses because tiny amounts dripping into the eye from hitting the forehead or other parts of the face may be sufficient to cause incapacitation. There were, however, no reports of a persistent irritant effect to the eyes. The officers are trained to aim for the brow, so that the spray can run into the eye, and officers undergo extensive training to ensure accuracy. In the cases where it is not effective, the subject is usually mentally disturbed or under the influence of alcohol or drugs, substances that reduce response to riot control agents, as discussed above. In some cases, these subjects literally felt no pain from the spray, but eye pain developed later as the subject returned to a normal mental state. There have been no reports of tolerance developing, even in an individual sprayed with the agent in 10 separate incidents.

Subjective data from Hertfordshire police reported that a concentration of 0.01% was too weak, because some highly agitated subjects, or subjects under the influence of alcohol and/or drugs could "fight through" the effects of the spray and avoid incapacitation. No information was available on the percent effectiveness at this concentration. Follow-up questionnaires sent 9 months after the tests reported no ill effects, but the details of the questionnaires were not available. Although a concentration of 0.64% was used in Zurich, this concentration was considered too high. No information could be obtained on effectiveness and health effects at this higher concentration, and no details were available regarding the rationale for this decision. An operational concentration of 0.3% was chosen, based in part on the over-the-counter availability of creams containing 0.4% PAVA. These creams are used as counter-irritants and desensitizers for arthritis and chronic pain.

Based on these results, eye effects of PAVA are considered SE 1 effects. Very incomplete concentration-response data are available, with 0.3% corresponding to >90% effectiveness in people hit in the face by the spray, and lower, but undefined effectiveness at lower concentrations. Insufficient data were available to identify a threshold for eye pain in bystanders or users (also SE 1). The available data include the report of violent pain when capsaicin was instilled into the rat eye at 50 μg/L (Jancso et al., 1968) and an EC_{50} in the guinea pig blink test of 46 μg/L reported for PAVA by Battensby et al. (1981). Although these two concentrations are very close, both reflect responses well above an irritancy or pain threshold. Although one properly should adjust the capsaicin data to account for the differences in molecular weight between PAVA and capsaicin, this difference is much smaller than the uncertainty in the threshold itself, and so no adjustment is made here.

3.4.3 Ethanol

The eye effects of ethanol have been reviewed by Grant (1986), ACGIH (2001), and NIOSH (2005). Eye irritation can result from contact of ethanol with the eye, either as liquid droplets deposited in the eye, or as a vapor. Ethanol droplets in the eye cause

an immediate burning sensation and blepharospasm (involuntary eye shutting). The acute pain is very short-lived, but discomfort may last for as much as two days, resulting from a feeling of a foreign body in the eye.

Several studies on vapor concentrations causing eye irritation in people have been conducted. In an early study involving exposure to ethanol vapor at concentrations of 0.7-1% (7000 – 10,000 ppm; 13,000 – 19,000 mg/m^3), subjects reported an unbearable odor that decreased with time, and eye irritation that began to burn with increasing intensity after several minutes, but did not further increase over the course of a 1-h exposure (Loewy & Heide, 1918). No irritation was noted in this study at 0.25% (2500 ppm, 4700 mg/m^3). In a controlled human study, a concentration of 15,000 ppm (28,000 mg/m^3) was described as causing "continuous lachrymation and coughing in people" (Lester & Greenberg, 1951, p. 169), but the duration of evaluation was not reported. This study also reported that concentrations of 5000 – 10,000 ppm (9400 – 19,000 mg/m^3) caused coughing and "smarting" of the eyes and nose, with symptoms reversing within the first few minutes. No eye or respiratory tract irritation was observed below 5000 ppm. Based on the Lester and Greenberg (1951) study, ACGIH set the TLV-TWA at 1000 ppm (1884 mg/m^3). No exposure durations were available for most of the studies, although it appeared that the reported effects occurred rapidly.

The only quantitative data located regarding concentrations of ethanol liquid in the eye that cause irritation to humans was a report that splashes of alcoholic drinks (e.g., whiskey, brandy, gin, or vodka) containing 40 to 50% ethanol caused immediate "smarting", but only superficial injury. Discomfort and hyperemia (increased blood in the area) were also transient. Some quantitative data on the effects of direct contact of ethanol liquid with the eye are available from experimental animal studies. One drop of "full-strength" ethanol caused reversible injury to rabbit eyes, graded as 3 on a scale of 10 after 24 h. A concentration of 70% applied to rabbit corneas injured and temporarily loosened the corneal epithelium, but recovery was complete. It was not clear from the available information whether this was an *in vivo* or *in vitro* study. A concentration of 50% applied to rabbit eyes resulted in a mild reaction graded 20 on a scale of 100.

The eye irritation and hyperemia resulting from eye contact with ethanol liquid or vapor are SE 1 effects. No information was located about interactions with other eye irritants. Based on the report of splashes with alcoholic drinks, the concentration of ethanol in the PAVA device would be expected to cause transient eye irritation (an SE 1 effect), but this irritation would be less severe and more transient than the irritation from the PAVA itself.

3.4.4 Transient Changes in Intraocular Pressure (IOP) Following Local Ocular Exposure to Peripheral Sensory Irritants

An eye effect commonly seen when irritants (both inflammatory-inducing and peripheral sensory) come into local contact with the cornea and conjunctiva is an almost immediate transient increase in intraocular pressure (IOP). Studies on the effects of riot control agents on IOP in both animal and controlled human studies, together with a consideration of the mechanism of induction of the pressure changes and its pathophysiological significance, are described in greater detail in Appendix D. No studies were located on the effects of PAVA or OC on IOP in laboratory animals, in

humans exposed in controlled clinical studies, or in humans exposed in the context of crowd control activities. However, the fact that these materials cause both peripheral sensory irritant effects and, at higher concentrations, are capable of causing inflammatory/injurious effects on the eye, strongly suggests that OC and PAVA will produce prompt onset-short duration ocular hypertensive effects similar to those seen with other riot control agents. This conclusion is supported by current knowledge of the probable mechanism of the irritant-induced transient elevation in IOP.

From a medical perspective, the induced increases in IOP are generally briefly sustained and should not present any hazard to the majority of individuals. However, there is the possibility that those with incipient narrow-angle glaucoma may be precipitated into a first attack, and those with established glaucoma may experience an exacerbation (Ballantyne, 1977; Ballantyne et al., 1973). Since the incidence of glaucoma is around 2% (Lyle et al., 1968) and because most of these cases occur in people over the age of 40 years (Smith, 1958), it is likely that, in the context of most civil disturbances in which peripheral sensory irritant riot control agents are used, the number of vulnerable individuals will be small. However, ocular hypertensive effects are possible in the older population and it would be useful to conduct ophthalmologic screening of exposed older individuals. The only exception to the short duration of induced ocular hypertensive effects with peripheral sensory irritants is when the concentration in contact with the eye may cause ocular inflammation and injury. In these circumstances, there will be an initial increase in IOP, but with the onset of anterior segment damage the pressure will further increase and may be sustained (Ballantyne et al., 1973, 1977). Depending on the severity and duration, increased IOP may be SE 1 – SE 3. This endpoint was not evaluated in the dose-response assessment, due to the lack of concentration-response information specifically on OC, PAVA, or any capsaicinoids.

3.4.5 Pressure Injury to the Eye

Only limited data were located on the potential for pressure injury to the eye from exposure to the liquid spray. These data are primarily from studies of water jets or water toys delivering large droplets, and often large volumes of water. None of the identified studies conducted a thorough analysis to determine the appropriate dose metric to describe the potential for injury to eye regardless of the type of stream, but preliminary work by Stuhmiller (1999) found that pressure was a better descriptor of effect than force.[7] This conclusion is supported by the analysis of A. Hepper (personal communication, November 2, 2004), which reviewed the potential for eye injuries from water jets in terms of pressure. Stuhmiller (1999) went on to note that the impulse pressure (a measure of transient pressure) from individual droplets was a much better predictor of effect than the average steady state pressure.

The two most reliable studies identified were conducted using cadaver pig eyes as a model system. In a preliminary unpublished study, Stuhmiller (1999) tested the effects of water jets from three different nozzle sizes on a total of 40 pig eyes at distances of 3.25-13 in. A 5-level qualitative pathology scale was used to grade the injuries. Levels 0 and 1 caused no effect and iris contraction, respectively, corresponding to SE scores of 0 and 1, respectively. The remaining 4 levels were all graded as serious injuries, with 2 = corneal damage or tear, 3 = hemorrhage, 4 = anterior chamber (not further described), and 5 = lens dislocated. These effects are all considered SE 3 effects, due to the potential for loss of vision. There was considerable scatter in the dose-response curve for pressure vs. injury score based on different jets and different eyes tested (Figure 2). However, the data appear to identify a threshold of 20 psi for SE 1 effects. This value corresponds to the lowest dose open square on the Injury Score 0 line in the figure and represents the NOEL for minimal effects. A threshold of 38 psi for SE 3 effects is identified. This value corresponds to the second open triangle on the Injury Score 1 line and is the NOEL for severe effects. In another study (Wong & Scribbick, 2000), fine water streams from two water toys were tested, with average pressures of 12 psi at close range. Large corneal abrasions and hydroinjection of orbital tissues were observed. No dose-response was available from this study, and further information on the distance tested was not available. These pressure measurements likely reflect steady state force, and impulse force would be much higher (J. H. Stuhmiller, personal communication, November 2, 2004). This suggests that the results of Wong and Scribbick (2000) are not inconsistent with the results of Stuhmiller.

[7] The preliminary finding was that eye injury was most like related to the high pressure impacts of individual droplets, rather than the steady dynamic force of the liquid stream. Because it was not practical to characterize the impact of individual droplets, an estimation technique was used. For some streams, such as that from a SuperSoaker toy used as a test delivery device, the droplets were large enough to cover the small pressure transducers, so that the pressure transducer output was considered to accurately reflect the impact pressure. For the fine nozzles, the droplets are smaller than the transducers, so the local impact pressure is understated. The authors assumed that the true impact pressure was the observed pressure corrected for the size of the droplet, as shown in Figure 2.

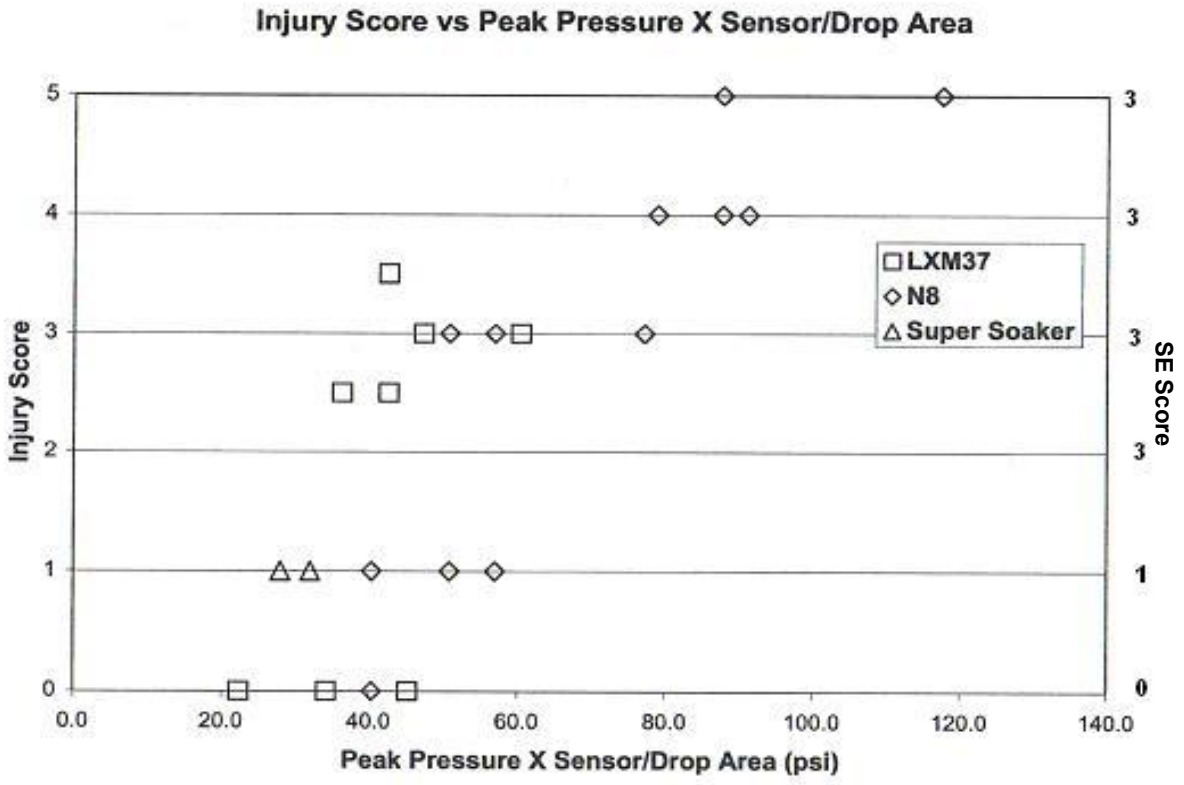

Figure 2. Dose-response curve for droplet pressure vs. injury score based on different jets and different eyes tested (Stuhmiller, 1999). Intermediate injury scores reflect the average of two eyes.

The SE 1 threshold identified by Stuhmiller appears to be consistent with a report on consumer products summarized by A. Hepper (personal communication, November 2, 2004). This report described two cases of non-permanent eye injuries (hyphema, or blood in the anterior chamber of the eye) in children from a water toy, reported to the U.S. Consumer Product Safety Commission (CPSC). Additional information from the CPSC reports could not be located on the CPSC web site. According to Hepper, the ophthalmologist in the cases stated that there was no information to determine the pressure on the eye that would cause injury, but a pressure-reducing valve that limited the outlet pressure to 1.7 bar (25 psi) was installed and was judged as safe. These measurements are likely to be in terms of steady state force. Other studies reviewed by A. Hepper (personal communication, November 2, 2004) noted that pressures of 10 bar (145 psi) are consistently associated with eye damage resulting in impairment of vision, including hemorrhage, increased intraocular pressure, and iris sphincter ruptures.

Limited data on pressure injuries to the eyes in actual use scenarios were available. A pressure injury to the eye (not further described) resulted, and healed completely. Holopainen et al. (2003) reported a case where exposure to an OC spray manufactured in Estonia (containing capsaicin, dihydrocapsaicin, with dichloromethane as the solvent and 1,1,1,4-tetrafluoroethane as the propellant) at 5 cm for 20 s resulted in sustained decrease in visual acuity, with visible scarring, and temporary loss of corneal transparency. Irrigation of the eye was delayed for a day after exposure. It was

not clear which of the observed effects were due to the OC and solvent and which (if any) were due to the force of the spray. Due to the lack of sufficient exposure information in these cases of pressure injuries, they will not be used in the dose-response assessment. Instead, the dose-response assessment will be based on the thresholds identified by Stuhmiller (1999).

3.5 RESPIRATORY EFFECTS

Respiratory effects are addressed in greater depth than the other effects in this assessment, because they are potential critical effects for evaluating effectiveness and risk. This section addresses the pharmacological and toxicological effects of the capsaicinoids on different regions of the respiratory tract, as well as the pulmonary risk from liquid aspiration.

3.5.1 OC and Capsaicin

Capsaicinoids are highly irritating to the respiratory tract, affecting the extrathoracic (nose and throat), tracheobronchial, and pulmonary regions. Observed effects of inhalation exposure include sneezing and coughing, shortness of breath, and bronchoconstriction. High pulmonary doses can cause pulmonary edema and respiratory arrest (Olajos & Salem, 2001). The potential for, and degree of, respiratory tract irritation in different regions is determined by both the aerosol droplet size and the concentration of capsaicinoids in the droplet. The effects of capsaicinoids on the respiratory tract are addressed in this section, with the discussion organized by the three major regions of the respiratory tract. According to U.S. EPA (1994), these regions are (1) the extrathoracic (ET) region (also called head region), including the nose, mouth, laryngopharynx, and larynx; (2) the tracheobronchial (TB) region, including the trachea, bronchi, and bronchioles; and (3) the pulmonary (Pu) region, including the respiratory bronchioles, alveolar ducts and sacs, and alveoli.

Stopford and Sidell (2004) reviewed the data related to nasal effects of capsaicin. Capsaicin can cause mucous production and a runny nose, but it is also used to treat vasomotor rhinitis (congestion of the nasal mucosa in the absence of infection or allergy). Repeated exposures to capsaicin desensitize the nasal mucosa, resulting in long-term decrease in nasal congestion. Initial nasal symptoms from capsaicin have been reported at doses as low as 250 pg[8] (0.25 E-3 μg)[9], and overt pain occurs at 15 μg. Intranasal doses up to 100 μg have been used for medical purposes. (These doses presumably refer to total mass inhaled, not the dose deposited in the region of interest.) The highest concentration of capsaicin in the dosing solutions in controlled laboratory studies (1 mM, or 0.03%) is a factor of 6-100 lower than the concentration of capsaicinoids in most OC products, which are typically in the range of 0.18-3% capsaicinoids. Presumably the reason for testing lower concentrations in the laboratory setting is to avoid unnecessary pain to the test subjects, while the higher concentrations

[8] A picogram (pg) is 10^{-12} gram.

[9] For ease of presentation and dose conversions, all doses are presented both in the form provided by authors, and converted to a consistent set of units, the microgram (μg, or 10^{-6} gram). Doses are expressed, for example, as 4E-4 μg, rather than 4 x 10^{-4} μg.

are used in law enforcement due to the uncontrolled nature of the dosing and the desire to ensure a response. This suggests that nasal pain would occur with OC products used in law enforcement.

A review by Recer et al. (2002) identified the lowest effective dose for nasal pain in an acute nasal challenge as 4.2E-3 mg (4.2 μg) (Greiff et al., 1995) or 4.6 E-4 mg (46 μg) (Stjarne et al., 1989). Table 1 of Appendix E presents some conversions between concentration of capsaicin in aerosols and inhaled dose that can be used to put these numbers in context. Nasal pain is an SE 1 effect. However, this effect was not included in the quantitative assessment, because respiratory effects are of greater concern for SE 1 effects from small aerosol droplets, large droplets would not be deposited in the nasal passage via inhalation (although they could be directly deposited in the nose from the spray), and nasal effects are not considered to be incapacitating.

Due to the effects of capsaicin on cough centers, a number of studies have used capsaicin provocation as an objective measure for evaluating sensitivity to chemical irritants. However, a number of factors, including differences among the study protocols and incomplete documentation of quantitative aspects of the protocols, complicate comparisons among these studies and quantitative use of these studies in this HERC. Many of the studies used single breath inhalation, or exposure for only 15 seconds to a minute, while the longest exposure located was for 6 min (see Table 1 of Appendix E). The single-breath studies may closely approximate the scenario from the stream or cone devices, but the aerosol droplets from those devices are often too large to be inhaled, and the illustrative assessment for this HERC was based on a cone spray consisting of large droplets. The 5-minute exposure falls within the likely range for the fogger devices, but actual exposures may be longer (see Section 5). A second difference among studies is in the definition of threshold, with many defining the threshold of effect as 5 coughs (C5), while others defined it as 2 coughs (C2). Some of the studies allowed additional analyses by providing data on concentration vs. number of coughs, but only one study (Doherty et al., 2000) provided information on the number of responders vs. concentration. In the absence of such incidence data, information about the population concentration-response (e.g., concentrations with near-100% response and a population threshold for response) was gleaned primarily from additional statements in the text of the studies. An additional problem is that, while the studies provided information on the concentration of capsaicin in the aerosolized solution, other quantitative details (e.g., aerosol droplet size, flow rate from the nebulizer) were often missing. The approach for calculating dose to the respiratory tract regions, and for addressing limitations in the data, is described in Appendix E. Coughing and associated shortness of breath is an SE 1 effect.

Law enforcement officers using OC devices delivering smaller aerosols described the gasping respiration and associated fear as the primary incapacitating action of OC. They also noted that it is difficult to quantitate incapacitation from these effects, since the fear response lessens with familiarity with the agent (e.g., resulting from repeated exposure), and the subject can learn to “fight through” the physiological effects. No direct quantitative concentration-response measurements for the gasping respiration were located. However, the cough response was judged to be a reasonable surrogate, as a measure of respiratory irritation. A more direct surrogate could not be identified, due to the differences between medical evaluation of responses and the

imprecise lay description of observed effects, coupled with the absence of data on aerosol droplet size for the device of interest for which these effects were reported. A limitation to this approach is that, although repeated coughing from capsaicinoid exposure impairs the ability to take a deep breath, the controlled studies generally noted that coughing stopped when the inhalation exposure stopped. In addition, several studies (Collier & Fuller, 1984; Blanc et al., 1991) reported no decrements in pulmonary function measurements taken immediately after exposures that caused coughing, and Blanc et al. (1991) noted experimental studies by other authors indicating that cough and bronchoconstriction occur via different pathways. Stopford and Sidell (2004) reviewed the data on respiratory effects of inhaled capsaicinoids, and reported that doses of approximately 1.5 μg (presumably total mass inhaled to the respiratory tract, not deposited dose) consistently produced a cough response across subjects. (See Table 3 for comparison with other studies.)

Several studies evaluated cough response in subjects that inhaled nebulized capsaicin for 1 minute. Additional study details are provided in Appendix E, and thresholds identified in these studies are summarized in Table 3. Midgren et al. (1992) exposed 26 normal subjects to varying concentrations of nebulized OC via a mouthpiece for 1 minute. Coughing started nearly immediately and decreased within the first 30 s of inhalation. The study authors stated that the individual cough thresholds (defined as 2 or more coughs) ranged from 0.016 to 10 μM, and the first concentration producing a statistically significant increase in the average number of coughs was 0.4 μM. The wide variability in individual thresholds reflects the wide human variability in irritation. However, the variability at the low end of the scale does not affect the conclusions for this study, since the focus for irritation is on the concentration (and thereby, deposited dose) that affects nearly all of the population. At the highest concentration (50 μM), some subjects could not take a full breath because of severe coughing, but coughing stopped immediately after the end of capsaicin inhalation, there were no objective signs of pharyngitis or laryngitis on visual examination, and there were no complaints of breathlessness.

Table 3. Summary of Studies Relevant to Thresholds for Respiratory Effects

Study	Aerosol Concentration		Amount Inhaled (µg)	Deposition (µg)			Effect
	µM	mg/L		Head	TB	PU	
Human Studies with Capsaicin or PAVA							
Blanc et al. (1991)	3	0.92	0.012	0.0025 - 0.0029	0.0021 - 0.0025	0.0032 - 0.003	One capsicum worker had >20% decrease in FEV_1 (bronchoconstriction)
	6	1.8	0.024	0.0051 - 0.0058	0.0043 – 0.0049	0.0059 - 0.0063	Lowest concentration at which all subjects coughed
Cho et al. (2002)	250	76	1.9	0.42	0.37	0.52	No bronchoconstriction in normal or asthmatic subjects
Collier and Fuller (1984)	4	1.2	0.61	0.38-0.43	0.056	0.079-0.1	All subjects coughed
Doherty et al. (2000)	31	9.5	0.085	0.021	0.029	0.021	Median cough threshold (C5) in COPD
	62	19	0.17	0.042	0.058	0.041	Median cough threshold (C5) in asthmatics
	500	**150**	**1.4**	**0.34**	**0.47**	**0.33**	**Cough threshold (C5) reached in approximately 45% of normals**
Fujimura et al. (1993)	8	2.4	0.13	0.029	0.028	0.023	Cough threshold (C5) caused no bronchoconstriction in normals, or subjects with asthma or bronchitis
Fuller et al. (1985)	10	3.1	0.073	0.019	0.018	0.012	Decreased specific airway conductance
Hathaway et al. (1993)	**1**	**0.3**	**0.15**	**0.034**	**0.033**	**0.027**	**Highest concentration not causing bronchoconstriction in any subject**
	10	3	1.5	0.34	0.33	0.27	Lowest concentration causing bronchoconstriction (>20% decrease in FEV_1) in asthmatics
	1000	300	150	34	33	27	No bronchoconstriction in normal subjects
Ind et al. (2001b) (PAVA)	3300	1000	6	1.3	0.85	1.9	No significant decrease in FEV_1 in asthmatics
Midgren et al. (1992)	10	3.1	1.5	0.35	0.33	0.27	Lowest concentration at which all subjects coughed
Animal Studies							
Reilly et al. (2003a); Crouch et al. (2003)	**N/A**	**N/A**	**625**	**113-222**	**54-66**	**79-87**	**Inflammation, no hemorrhage or necrosis**
DeBarre et al. (1999)	N/A	N/A	150 mg/m^3 in air	N/A	1.5	3.4	No effect on minute volume; mucus secretion and interstitial edema

TB = tracheobronchial region; Pu = pulmonary region

Ranges of estimates for regional deposited dose reflect the results of sensitivity analyses; see Appendix C for more details. Exposure for the animal studies was expressed as either concentration in air (DeBarre et al., 1999) or dose deposited in the respiratory tract (Reilly et al., 2003a), and so the aerosol concentration is N/A (not applicable).Studies and doses used as the basis for the quantitative assessment are bolded.

Using a similar study design, Collier and Fuller (1984) exposed volunteers for an unspecified period to nebulized capsaicin generated from solutions 2-65 μM. All 17 subjects (13 non-asthmatics, 4 asthmatics) coughed at concentrations of 4 μM and higher; there was no clear difference in sensitivity between asthmatics and healthy subjects. The coughing continued throughout the challenge exposure, but stopped within minutes of discontinuing exposure. Despite the coughing, there was no effect on the FEV_1 and no shortness of breath. However, both were measured a minute or more after the end of the exposure. This indicates no prolonged effect on pulmonary function, but highly transient effects may have been missed. Capsaicin delivered through the nose also caused coughing. The cough response was abolished by local anesthesia to the pharynx and vocal cords.

In contrast to these results, a number of more recent studies have documented enhanced sensitivity to cough in subjects with respiratory disease. Doherty et al. (2000) used a protocol involving a single deep inhalation to investigate the cough threshold (concentration causing five or more coughs, C5) in 96 normal subjects, 53 subjects with chronic stable asthma, and 57 subjects with chronic obstructive pulmonary disease (COPD). They found that the median C5 was 31 μM in the COPD subjects, 62 μM in the asthmatics, and >500 μM in the normal subjects. (The highest concentration tested was 500 μM, resulting in a response of approximately 45% in the normal subjects.) Cho et al. (2002) reported individual cough thresholds (defined as the concentration of capsaicin causing at least 5 coughs) in chronic cough patients (including patients with cough variant asthma) that were factors of 10 to 1000 lower than the thresholds for normal patients, but did not present data on the concentrations that caused cough in all subjects in any group. Extrathoracic airway hyper-responsiveness (decreased peak inspiratory flow) was observed in some of the chronic cough groups. The authors suggested that hypersensitivity of the extrathoracic airway could result in both chronic cough and increased cough sensitivity. (Note that this is separate from the hyper-responsiveness to bronchoconstriction described below.) Millqvist (2000) reported that asthmatics coughed more intensively than normal subjects, but information on comparative concentration-response was not available.

In a study of cough following inhalation of a single breath of capsaicin where subjects were instructed to inhale deeply, Blanc et al. (1991) tested concentrations of 0.3-6 μM in a group of capsicum workers and unexposed administrative workers, and found that the lowest concentration at which cough was elicited in all subjects was 6 μM, with no difference between the groups in the highest concentration to induce cough. Although threshold was defined as any cough, rather than the lowest concentration to produce a specified number of coughs, the authors reported that the median number of coughs at the threshold was 2.5 and 3 in the exposed and unexposed workers, respectively. It is not clear why the threshold identified in this study was so much lower than that in other studies, although a slight difference could result from the smaller number of coughs at threshold. The pattern of cough thresholds was bimodal for the exposed workers, but it was not clear if some of the difference in response between the groups was related to differences in group characteristics, such as higher dietary preference for spicy foods, or higher smoking, or due to the chronic capsaicin occupational (inhalation and dermal) exposure. One of the subjects in the cough study exhibited a 24% decrease in FEV_1 at 2.9 μM.

A number of other studies (Choudry et al., 1989; Fujimura et al., 1992, 1993; Millqvist, 2000; Cho et al., 2002) measured cough from capsaicin, but did not provide information that can be used to evaluate what concentration causes cough in most people. Some of these studies focused instead on the lowest concentration that can cause cough.

The region of the respiratory tract where capsaicin acts to induce cough is important in the determination of the deposited dose (see Appendix E). Multiple regions appear to be involved. Fujimura et al. (1992) noted that both the larynx and tracheobronchial tree contain non-myelinated C fibers (the nerve fibers believed to be responsible for capsaicin-induced cough), and suggested that inhaled capsaicin causes cough by acting on the larynx, trachea, and major bronchi. In support of this supposition, they noted that coughing is induced in patients with the larynx removed after inhaling capsaicin through a tracheostomy tube. This action in multiple regions may explain some apparently conflicting data in other studies. While data from the anesthesia exposure of Collier and Fuller (1984) indicated that coughing was determined by dose to the pharynx and vocal cords (ET region), Hansson et al. (1992) used a similar protocol and aerosol droplet size with a radiolabeled marker, and found that <5% of deposition was to the trachea or larynx, with approximately 40% depositing to the Hilar lung region and 50-60% depositing to the peripheral lung region. They noted that the regional deposition depended on both the aerosol droplet size and the inspiratory flow rate. Hansson et al. (1992) suggested that these results indicate that the cough response is triggered at a point below the trachea, and that the local anesthesia by Collier and Fuller (1984) resulted in anesthetic fumes reaching the lungs. In contrast to the results of Hansson et al. (1992), Barros et al. (1991) found that decreasing the inspiratory flow rate increased the number of coughs, even though the inhaled volume was lower. They suggested that lower flow rates resulted in more deposition in the higher regions of the respiratory tract, particularly the larynx.

While the cough response may be the intended effect for certain use scenarios, prolonged coughing that precludes the subject taking a deep breath could lead to severe effects, due to oxygen deprivation. This coughing does not involve copious mucous secretions and no study has reported an effect on oxygen saturation. However, few studies evaluated this endpoint, and the located cough studies generally involved exposures of 1 minute or less (although Millqvist (2000) used a 6-minute exposure protocol), compared with exposures for 10 min or more that may be relevant to fogger scenarios.[10] In addition, concerns have been raised that asthmatics may be more sensitive to bronchoconstriction from capsaicinoid inhalation. Bronchoconstriction in asthmatics can be life-threatening. Indeed, the few cases for which in-custody deaths have been attributed to OC exposure have involved asthmatics or other individuals with compromised respiratory function. Therefore, several studies have specifically investigated the respiratory effects in asthmatics. Bronchoconstriction is an SE 1-3 effect, depending on the severity; this analysis focused on SE 2 bronchoconstriction in clinical human studies of asthmatics, as the most sensitive unintended effect for this scenario.

[10] Based on this concern, it has been suggested that additional information be obtained on this issue, and that oxygenation of the blood be monitored in subjects exposed to OC or PAVA aerosols of small droplets, as noted in Section 6.

In a study designed to evaluate the relative sensitivity of asthmatics and normal subjects, Hathaway et al. (1993) exposed 10 normal subjects and 17 asthmatics to nebulized capsaicin for 1 minute.[11] The patients were exposed to 10-fold increasing concentrations of capsaicin from 3E-6 to 0.3 mg/mL of solution (0.01 – 1000 μM), and the maximum drop in FEV_1 was recorded. There was no effect on FEV_1 in the normal subjects, but seven of the asthmatic subjects exhibited bronchoconstriction, ranging from a 10% to 40% decrease in FEV_1. Two subjects experienced a >20% decrease in FEV_1, at 0.03 and 0.003 mg/mL of capsaicin, respectively. These concentrations in the starting solution define SE 2 effect levels, with a sub-threshold concentration of 3E-4 mg/mL (1 μM). Coughing (not further quantitated) was reported in all subjects, with no apparent difference between those who experienced bronchoconstriction and those who did not. However, no information was provided on the concentrations that induced cough. Interestingly, there was no relationship between the response to capsaicin and methacholine (a standard challenge agent) among the asthmatics, indicating separate mechanisms, and that the methacholine response cannot be used as an indicator of sensitive populations.

Fuller et al. (1985) used a single breath design to evaluate the bronchoconstriction response to capsaicin. Subjects inhaled a single breath of nebulized capsaicin from a 1E-4 or 1E-5 M (10-100 μM) solution, followed by a measurement of specific airway conductance. Bronchoconstriction was maximal at 10 s, and returned to baseline within 60 s of the exposure. While the medical significance of reversible bronchoconstriction of such short duration is trivial, the exposure in this study was only for a single breath; more significant effects could occur with more prolonged exposure. This study could not be compared directly to other studies of bronchoconstriction, because FEV_1 was not reported. The authors reported no difference among normal subjects, smokers, or mild asthmatics, but review of the graphs suggested that the mild asthmatics had a tendency toward a somewhat larger response at the high dose.

As noted above, one of the capsaicin workers in the Blanc et al. (1991) study exhibited a 24% decrease in FEV_1 following a single-breath inhalation test with 2.9 μM capsaicin. In a test of 77 chronic cough subjects and 15 controls who inhaled a single breath of capsaicin up to 250 μM (76 mg/L), Cho et al. (2002) found no subjects with a 20% or greater drop in FEV_1. Fujimura et al. (1993) measured FEV_1 in 11 subjects with asthma, 10 subjects with chronic bronchitis, and 14 normal subjects before and after a 15-second inhalation of capsaicin at the cough threshold (C5)[12]. The authors reported that capsaicin at the cough threshold caused a statistically significant decrease in FEV_1 in the subjects with bronchitis or asthma, but not the normal subjects. However, none of the means decreased by 20%, and so these concentrations are considered no-effect levels for bronchoconstriction for the purposes of the current assessment. The authors did not provide any information on whether there were hyper-responsive individuals. Doherty et al. (2000) did not measure FEV_1 following capsaicin challenge, but noted

[11] Subjects had been exposed to a standard methacholine bronchial provocation test 2 h prior to capsaicin exposure. Presumably this prior challenge did not affect the capsaicin results, but this presumption could not be verified.

[12] The authors did not specify which cough threshold (individual or geometric mean for the group).

that the cough threshold (C5) was not related to the level of bronchial hyper-reactivity, based on the results of histamine challenge studies and the use of bronchodilators.

Despite the repeated exposures to capsaicin, the only report of tachyphylaxis in the controlled clinical studies investigating respiratory effects of capsaicin was Fujimura et al. (1992), who found decreased cough sensitivity for at least an hour after exposure of subjects with sinobronchial syndrome, but no tachyphylaxis in normal subjects.

A number of modifiers of sensitivity to cough have been identified. Chronic obstructive lung disease and upper respiratory tract infection increase sensitivity to capsaicin-induced cough (Stopford & Sidell, 2004; O'Connell et al., 1996), while co-exposure to systemic opioids decreases sensitivity (Fuller et al., 1988). Females were found to have a lower capsaicin cough threshold than males, a difference that did not appear to be due to differences in height or weight (Fujimura et al., 1996). As noted above, several recent studies also suggest that asthma increases the cough sensitivity (Doherty et al., 2000; Cho et al., 2002; Millqvist, 2000; Stopford & Sidell, 2004), although earlier studies did not see such a difference (e.g., Collier & Fuller, 1984). However, general allergenicity (atopy) in nonasthmatic subjects was not a determinant of cough sensitivity (Fujimura et al., 1998).

In a retrospective evaluation of 81 people who came to the emergency room after exposure to OC (5% Cap-Stun spray) in law enforcement confrontations, respiratory symptoms in 12 asthmatics were reported as being similar to those in the rest of the population (Watson et al., 1996). Five patients (two of whom were asthmatic) presented with shortness of breath or wheezing, but all resolved without treatment.

Limited data are available on the respiratory effects of long-term occupational exposure to capsaicinoids. These studies typically reported initial respiratory symptoms similar to those seen with acute exposure (e.g., cough, runny nose, sneezing). These symptoms decreased, and often were completely reversed, with continued exposure. Blanc et al. (1991) conducted a study of 22 hot pepper workers chronically exposed to hot chili powder and 19 unexposed workers in the same plant. No information was available on exposure levels. Chronic cough was reported in 59% of the exposed workers, compared to 21% of the controls. The exposed workers also had more common complaints of chest discomfort, shortness of breath, and stuffy or runny nose, but fewer complaints of sinus trouble. There was no tachyphylaxis or significant decrease in baseline pulmonary function in either group. Asthmatics did not react differently from the other workers. Another study of occupational exposure evaluated 61 male spice grinders in Singapore for skin or respiratory symptoms (Chan et al., 1990). Respiratory symptoms (upper respiratory tract irritation, sneezing, runny nose) were reported during work by 49% of the workers. Reactions were the strongest during the first week, and disappeared with continued exposure in half the affected workers. Dust levels were reported as 0.03 to 0.82 mg/m^3, with about 45% of the dust being respirable. Stopford and Sidell (2004) estimated that the mean capsaicinoid exposure was 0.8 $\mu g/m^3$ and the maximum was 4 $\mu g/m^3$. Lankatilake and Uragoda (1993) evaluated pulmonary function in 25 men who had worked in chili grinding factories in Sri Lanka for an average of 6.6 years. Pulmonary function measurements in the exposed workers were not different from the values for controls, and there was no difference between the pre- and post-shift pulmonary function measurements in exposed workers after a weekend of no exposure. The authors noted that 60% of the workers had

respiratory symptoms including cough when they first started work, but the symptoms waned after 3 weeks – 6 months of employment. Exposure to respirable dust was reported as 0.11 – 0.52 mg/m^3 based on personal sampling. Adjusting for a capsaicinoid content of 250 mg/100 g dry weight in the variety of chili peppers processed at the factory, the exposure to capsaicinoids in respirable dust was 0.28 – 1.3 μg/m^3.

Two published reports of life-threatening (SE 3) respiratory effects were located for OC sprays. While these case reports suggest that deliberate inhalation of large amounts or high concentrations of OC can be fatal, there is insufficient information in the case reports to definitively attribute the effects to OC, rather than to the solvent(s). Because of this uncertainty, it is not appropriate to use these studies directly in a risk assessment. Effects of solvents are addressed further in Appendix B. In the first case (Billmire et al., 1996), a 5% OC spray was discharged accidentally in the face of a 4-week-old infant. No information was provided on the volume released. There was a rapid onset of gasping respirations and epistaxis (profuse nosebleed), followed by apnea and cyanosis. The infant was treated with mechanical ventilation and extracorporeal membrane oxygenation, and survived. The study authors stated that tracheal exudate during the course of treatment and recovery was similar to the clinical course in adult patients of fatal necrotizing tracheobronchitis after exposure to CN or CS. The study authors did not provide further details or information on the comparison to CN and CS. In the second case (Winograd, 1977), an 11-year-old boy deliberately deeply inhaled an OC spray from the jet of the spray. He initially coughed for almost an hour, and then became asymptomatic. Four hours later he developed respiratory distress, and noncardiogenic pulmonary edema that progressed to respiratory arrest and required intubation. The boy recovered with treatment. This case illustrates the potential for a delayed pulmonary response, with extremely high doses of inhaled OC, as well as the potential for deep lung effects in people.

Although a number of animal studies have evaluated respiratory effects of capsaicinoids, relatively few provided useful dose-response information. A subset of the studies is summarized here.

Only one study was located that evaluated respiratory tract histopathology (Reilly et al., 2003a; additional details and related studies are reported in Crouch et al., 2003). This study evaluated the effect of small aerosols of capsaicinoids on anesthetized male Sprague-Dawley rats (125 g body weight). OC canisters were fully discharged into a closed container and the capsaicinoids and other non-volatiles were reconstituted in ethanol. To maximize the dose to the lower respiratory tract, aerosols were generated using a nebulizer that typically resulted in 85-90% of the aerosol droplets having an aerodynamic diameter between <0.6 and 2.9 μm. The rats were exposed nose-only for 30 min, and the delivered dose was measured using a filter that collected the aerosol at the nose. The delivered dose was calculated using a minute volume of 0.2 L/min and a deep lung deposition factor of 10%. The rats were sacrificed 24, 48, or 72 h after exposure, and histopathology was evaluated using a graded analysis.

The rest of this description refers to the unpublished dose-response information provided by Crouch et al. (2003) and G. Yost (personal communication, October 26, 2004 and November 5, 2004); similar, but less detailed information was provided in the published report by Reilly. A total of 17 criteria (including necrosis, dysplasia,

metaplasia, cellular infiltrate, hemorrhage) were scored on a scale of 0 – 3 for each criterion, and the average histopathology score was reported. The study authors (G. Yost, personal communication, October 26, 2004 and November 5, 2004) noted that this approach meant that the absence of various endpoints resulted in low overall scores even in the presence of clear adverse effects. Thus, scores of about 0.5 reflect effects that would preferably receive medical attention (SE 2), including hemorrhage, alveolar emphysema, epithelial cell loss, inflammation (congestion and edema), and neutrophil cell infiltration. Results are presented in Table 4. Reilly et al. (2003a) used these data to report that low (0.07 mg/kg)[13] and intermediate (0.3 mg/kg) doses of capsaicinoids or OC sprays produced very mild or moderate lesions, respectively. Reilly et al. (2003a) considered the effects at 0.8 mg/kg and higher to reflect more severe and frequent lesions.[14] The effects were reversible within 48-72 h. As shown in the table, there were similarities in response for different OC products when normalized by dose, but differences across products remained even after this normalization, presumably due to differences in potency and non-capsaicinoid components of the various OC preparations. PAVA (nonivamide) had a generally similar potency to that of OC and capsaicin. The authors also stated that ethanol has been reported to potentiate the effects of capsaicinoids, but no effect was noted in the ethanol-only control. Preliminary data reported by Crouch et al. (2003) suggested that drugs of abuse (cocaine, methamphetamine) may increase the lung effects of capsaicinoids.

[13] Dose units as reported by the authors.

[14] Upper airway lesions included patchy epithelial necrosis and sloughing of cells in nasal turbinates and trachea, sometimes with inflammatory cell infiltrates. The most extensive lesions were in the air sacs and alveoli, including infiltrates of inflammatory cells, capillary hemorrhage, and occasional edema. Dose-response data were not provided for the descriptive histopathology, but these effects apparently all occurred at 1.0-1.2 mg/kg.

Table 4. Comparative respiratory inflammation of capsaicinoids to oleoresin capsicum, capsaicin, and OC sprays.

Treatment Groups	Deposited Dose[15]	Average Histopathology Score			
		Nasal Turbinate	Trachea	Mid Lung	Distal Lung
Controls					
Untreated control		0.08	0.02	0.08	0.08
Air only control (30 min; 24 hr)	90 ng/kg (0.011μg)	0.15	0.0	0.03	0.06
Ethanol only control (30min; 24hr)	340 ng/kg (0.04 μg)	0.0	0.05	0.0	0.06
Standardized Solutions					
Capsaicin 50 mg/mL (30 min; 24 hr)	1.0 mg/kg (125 μg)	0.13	0.12	0.455	0.53
(30 min; 48 hr)	1.0 mg/kg (125 μg)	0.23	0.06	0.44	0.5
10% OC (30 min; 24 hr)	0.8 mg/kg (100 μg)	0.135	0.12	0.335	0.44
(30 min; 48 hr)	0.8 mg/kg (100 μg)	0.26	0.12	0.35	0.53
OC Products					
Security Plus 10% OC (15 min; 24 hr)	0.07 mg/kg (8.75 μg)	0.03	0.09	0.29	0.53
(30 min; 24 hr)	0.1 mg/kg (12.5 μg)	0.0	0.08	0.5	0.55
911 10% OC (15 min; 24 hr)	0.3 mg/kg (37.5 μg)	0.06	0.09	0.14	0.32
(30 min; 24 hr)	0.5 mg/kg 63.5 μg)	0.18	0.08	0.62	0.50
Guardian 10% OC (15 min; 24 hr)	0.3 mg/kg (37.5 μg)	0.05	0.08	0.15	0.24
(30 min; 24 hr)	0.8 mg/kg (100 μg)	0.15	0.09	0.52	0.49
ChemArmor (15 min; 24 hr)	0.3 mg/kg (37.5 μg)	0.09	0.05	0.11	0.19
3.3% Nonivamide (30 min; 24 hr)	1.0 mg/kg (125 μg)	0.12	0.12	0.43	0.56

Adapted from Crouch et al. (2003). Note that the average histopathology score is the average across all effects, and does not reflect the severity of individual endpoints. **The dose used for the dose-response assessment (0.5 mg/kg) is based on the data for two rats, and so no average scores are available for that dose, and the data are not shown in this table.**

Identification of an effect level from these data is challenging, due to the absence of a clear dose-response and the use of average histopathology scores. These average scores meant that a mild effect (e.g., inflammation) affecting a large region was weighted equally with effects reflecting severe tissue destruction, such as necrosis or

[15] Deposited dose as calculated by the study authors using the approach described in the text. Calculation of regional deposited dose (i.e., dose deposited to the various respiratory tract regions) is described in Section 4.2 and Appendix E.

hemorrhage. For pulmonary effects[16], the focus is on SE 2 endpoints. Pulmonary effects are not related to effectiveness, and SE 1 effects in the target not related to effectiveness play only a minimal role in the assessment. Similarly, although SE 1 effects are of concern for users or bystanders, the threshold for tracheobronchial effects is so much lower than the doses tested by Reilly et al. (2003a) (see Section 4) that the dose to the tracheobronchial region of the respiratory tract would drive the assessment for users or bystanders, even at small aerosol droplet sizes. The NOEL for SE 2 effects was identified based on the report by Reilly et al. (2003a) that doses of 0.07 (not shown in table because detailed data were not available) and 0.3 mg/kg produced minimal and moderate lesions, while doses >0.8 mg/kg caused "more severe" lesions. These data were supplemented by individual animal data (for two rats out of an unspecified total) showing that **the only effect at 0.5 mg/kg was inflammation and related effects,** although the average histopathology score for these two animals was lower than the average score shown in Table 4; no further data at this dose were available. **Based on a body weight of 125 g reported for this study, this corresponds to a pulmonary dose of 62.5 μg, using the author's calculations for pulmonary deposition.** (This calculation is refined in Section 4.) However, this conclusion is limited by the limited amount of primary data that could be obtained.

In a study of the effect of OC on respiratory parameters in rats, Debarre et al. (1999) exposed male Wistar rats to an atmosphere of OC for 5, 10, 15, or 20 min in successive exposure scenarios, or solvent alone for 20 min. The atmosphere was generated by extracting the OC from an OC spray and creating a defined aerosol. The authors reported that 90% of the aerosol droplets had an aerodynamic equivalent diameter of 1.5-2 μm. Based on monitoring data reported by the authors, the exposure atmosphere was approximately 150 mg/m^3. Exposed rats had a decreased minute volume compared to pre-exposure, but the reduction was comparable to that seen with the solvent (not specified). The decrease in minute volume was caused by both decreased tidal volume and decreased respiratory frequency. Histopathology evaluation revealed increased mucous secretion and interstitial edema.

Capsaicin, particulate matter, and neuropeptides act synergistically to promote the production of inflammatory mediators in human respiratory epithelial cells *in vitro* (reviewed by Reilly et al., 2003a); a similar effect was noted for capsaicin and sulfur dioxide-induced inflammation *in vivo* (Long et al., 1999).

Using an ovalbumin-sensitized and challenged guinea pig model, Busker et al. (2001) found that exposure to 0.11 mg/m^3 capsaicin as a fine aerosol droplet (mean aerodynamic diameter 1 μm) for 10 min was lethal to 7/10 challenged animals. This was consistent with other findings that the guinea pig is very sensitive to lethal effects of capsaicin. The cause of death was severe bronchoconstriction. This concentration was not lethal to the normal guinea pigs, but 7.9 mg/m^3 killed half of the normal animals. As a more realistic simulation of an OC spray event, the authors also sprayed OC (Defense Technology, MK-4 OC concentration apparently 10%) in the face of the sensitized and normal guinea pigs for 1 or 4 s. Bronchoconstriction was observed, and the sensitized animals were more sensitive, but the effect was much milder than following the aerosol exposure. The difference between the two exposure conditions was attributed to

[16] As described above, the pulmonary region refers to the deep lung, and includes the respiratory bronchioles, and alveolar region.

aerosol droplet size, with most of the aerosol droplets >20 μm in the second case, and thus only negligible amounts could be inhaled.

The RD_{50} is the concentration of a chemical required to produce a 50% decrease in respiratory rate for sensory irritants. The response is mediated by the trigeminal nerve. Alarie and Keller (1973) reported an RD_{50} in mice for capsaicin of 10.4 mg/m^3. A much lower value of 0.2 mg/m^3 was reported by Morris et al. (2003), but with minimal documentation.

3.5.2 PAVA

A series of three unpublished controlled clinical studies investigated the respiratory effects of inhaling nebulized PAVA or capsaicin. These studies did not conform to Good Laboratory Practice (GLP) guidelines, but are included here because they are the only controlled clinical studies investigating some of these endpoints. These studies have the advantage that droplet size and concentration of the solution were reported, and the sensitivity of the studies was increased by using nebulized aerosols. However, because the subjects inhaled only one breath of PAVA at each dose level, extrapolation to longer exposure to a mist from a cone spray, or to a fogger that fills a room is limited, as described above. For each of the studies, pulmonary function was measured at baseline, and then the subjects were asked to inhale a single breath of PAVA or capsaicin from a nebulizer. The volume of aerosol inhaled was 5-7 μL and the mass median diameter (MMD) was 2-5 microns[17]; no geometric standard deviation for the aerosol droplet size distribution was reported. The same subjects received increasing concentrations of the test material. The number of coughs was counted, and airway resistance and FEV_1 were measured after coughing stopped.

In the first study (Ind et al., undated); capsaicin and PAVA were tested in 10 men (5 never-smokers and 5 ex-smokers) at concentrations that doubled with each exposure over a range from 0.5 μM to 500 μM at 1.5 minute intervals. After 15 min rest, the subjects were tested again with twice the concentration that produced 5 coughs (2xc5) or the highest concentration (c9). The actual concentrations were not reported for either capsaicin or PAVA. The response at c9 and 2xc5 was similar for the two chemicals, but it was not clear if this similarity was due to similar potency or due to the exposure measures being normalized based on response. There was a slight, but not significant increase in airway resistance with PAVA, and a slightly larger, but still marginal increase (average 23.4%) with capsaicin at the high concentration, although there was a large variability in response. Methacholine produced the expected increase in resistance. There was no significant effect on FEV_1, oxygen saturation, or blood pressure with either chemical. Heart rate changed by <5% with both capsaicin and PAVA; this change was not considered clinically significant. The authors reported that at the highest concentration tested, the subjects stopped inhaling fully, because the cough sensation was induced early in the inspiration. This cough reflex would limit the dose to the deep lung. The authors also noted marked subject variability in the cough reflex.

[17] The aerosol size was variously reported in the different studies as 3.5-4 microns or 2.8 microns, but the second author reported in response to clarifying questions that the same setup was used for all of the studies, and the aerosol size was quoted by the manufacturer as 2-5 microns. Further information was not available. (Watson, personal communication, September, 2004)

The same concentration that caused 6-7 coughs in some subjects caused no coughs in two subjects.

The second study (Ind et al., 2001a) tested concentrations of PAVA up to 0.3% (0.01 M, or 10,000 μM) in eight men and two women. There was a concentration-related increase in the number of coughs, except at the highest concentration, which was refused by two subjects. Both of the females coughed more than 7 of the 8 men, and both women refused the final test concentration. The sample size was too small to determine whether this difference was due to individual differences, gender-related differences, or the women feeling less motivation to withstand the discomfort of the testing. Insufficient information was provided to determine the concentration that caused cough in most of the subjects. Heart rate was increased by 15% at the second to the last dose, a response that was attributed to the violent coughing and burning sensation; this burning sensation was reported to decrease over 2-3 min. Blood pressure at the highest concentration was also increased by 5.7% (systolic) and 8.6% (diastolic). There was no significant effect on FEV_1 even at the highest concentration; airway resistance was not measured.

The third study (Ind et al., 2001b) tested eight male and two female mildly asthmatic subjects with normal lung function; subjects with unstable asthma were excluded. PAVA concentrations up to 0.10% (0.001 M, or 1000 μM) were tested. There was no significant effect on average FEV_1 from PAVA exposure up to the highest concentration, although FEV_1 was reported to fall in 6/10 subjects. Based on the initial report, two subjects appeared to have a decrease in FEV_1 of >20% (generally considered a biologically meaningful, adverse effect), suggesting that they may have reflected a sensitive population. However, individual data for these two subjects obtained from the investigators indicated that the decrease compared to the saline control was not clinically significant, at 10% or less for these subjects, and that the main study report reflected decrease from baseline. There was no effect on oxygen saturation even at the highest concentration. The heart rate and blood pressure increased by about 5-8% at the highest concentration in the testing of non-asthmatic subjects.

Based on these studies showing the beginnings of a trend of increased airway resistance, and non-clinically significant decreases in FEV_1, it is reasonable to expect that asthmatics may have increased sensitivity to decreased pulmonary function from sufficiently high doses of PAVA, as described above for capsaicin. The absence of an effect in this study may have been because of the relatively small sample size tested, or because sufficiently high doses were not tested, in light of the relatively small deposited dose in this single-breath study (despite the high test *concentration*). The study authors noted that they found only a minimal effect, but their results are not sufficient to conclude that a similar minimal risk applies to patients with severe asthma, those recovering from an asthma attack, or people with COPB. Indeed, the two subjects with the largest fall in FEV_1 were also the most sensitive to the bronchoconstriction effects of methacholine. However, no clinically significant effects were observed, even in asthmatics at the highest concentration tested. Information regarding the effect on airway resistance of prolonged exposure under a fogger scenario would be useful to clarify the potential effects. The dose to the deep lung in all of these studies was limited

by the cough reflex; no investigations were available regarding the effect of the reflex in a continuous exposure scenario.

In reviewing this study, the UK Committee on Toxicity (COT, 2004) noted that under operational use, subjects would be experiencing high levels of stress, which would increase the risk of clinically significant bronchospasm. However, subjective data from use of PAVA, delivered using a large aerosol droplet size, report no cases of bronchospasm, although no primary data were available for independent examination.

Lett (1996c) conducted an acute inhalation study of PAVA with groups of 5 male and female SPRD rats per concentration group exposed for 4 h. An atomizer was used to generate the exposure atmosphere, but no aerosol droplet size measurements were reported. The highest concentration tested was 170 mg/m^3 (4.8 E-7 M in air).[18] Significant irritation of the exposed groups resulted in the rats scratching their noses and mouths after removal from the exposure chambers. No other signs of toxicity and no change in body weight were reported. The rats were euthanized 7 days after the termination of exposure. No PAVA-related histopathology was found on the mucous membranes of the nose and throat, the cornea, retina, or bronchial tubes. The authors did not report conducting histopathology analysis of the pulmonary region of the lung, except that "any interesting tissues" identified in the macroscopic evaluation were also evaluated histopathologically. No such further examination was noted. The study was also compromised by effects observed in the control groups. Bleeding and infection of the lungs was observed in both exposed and control animals. Secretions from the tear ducts were observed in both control and exposed males.

As described in the previous section, Reilly et al. (2003a) reported significant histopathology in rats at lower PAVA exposure levels. The reason for the difference between the results of these two studies is not clear, but may be related to either differences in aerosol droplet size, or the 7-day recovery period in the Lett (1996c) study.

3.5.3 Ethanol

Inhalation of ethanol vapor can cause respiratory irritation and coughing. However, the large droplet size from the PAVA stream means that exposure of the respiratory tract from this device would be minimal. Therefore, quantitative data on irritation were not further explored. Reilly et al. (2003a) reported that ethanol can potentiate the irritant effects of capsaicinoids, but no quantitative information on this potentiation was located.

3.5.4 Reactive Airways Dysfunction Syndrome (RADS)

One potential effect that has not been reported in the current literature for OC is Reactive Airways Dysfunction Syndrome (RADS), which is a respiratory complication of pulmonary overexposure to an airborne irritant (inflammation-inducing) chemical, and was first described by Brooks et al. (1985). This syndrome develops after an acute

[18] This concentration was reported by the COT (2004) in their summary of the study as 3.6 mg/L, or 3600 mg/m^3. The reason for this discrepancy is unclear, although it may be related to unclear and confusing reporting of exposure in the original report.

inhalation exposure to moderately high concentrations of an airborne irritant (inflammation-inducing), and clinically presents as an asthmatic-like illness. Respiratory symptoms and airway hyper-reactivity may persist for several years after exposure. All materials that have been described as etiologic agents in the pathogenesis of RADS share the common characteristic of being irritant in nature. However, OC differs from the other chemicals in being receptor-mediated, acting through substance P. Overall, Ballantyne and Salem (2004) stated that it is anticipated that peripheral sensory irritant materials that also have the potential to cause pulmonary inflammatory changes will cause RADS. RADS has been described following overexposure to CS (Bayeaux-Dunglas et al., 1999; Hu & Christani, 1992; Worthington & Nee, 1999). RADS has not been described after exposure to OC alone, but symptoms typical of RADS (cough, chest tightness, wheezing and shortness of breath, with pulmonary function tests demonstrating reversible and fixed obstructive pulmonary disease) developed in an individual after an exposure for at least 30 second to Deep Freeze® in an enclosed space. Deep Freeze® contains 1% CS and 1% OC. Although not described as occurring after exposure to OC alone, the biological reactivity of OC suggests that RADS is a possible complication of inhalation over-exposure to OC, although the concentration at which this effect might occur is not known. Further information on whether exposure to high concentrations of OC is associated with RADS would be useful.

3.5.5 Aspiration of Liquid

A potential for lung damage resulting from liquid aspiration exists if the target is inhaling with an open mouth at the same time that the stream of OC or PAVA hits the mouth. Aspiration of a sufficient fluid can cause death by “dry drowning” (i.e., respiratory difficulties due to fluid in the lung without immersion in water), as a result of the deposition of liquid in the deep lung. Inhalation of a volume of 1-3 mL/kg of a water-based inert liquid significantly impairs gas exchange, and can cause acute respiratory distress syndrome. Symptoms include pulmonary hypertension and airway closure due to contraction of the musculature of the terminal bronchioles (Schmidt & Madea, 1995; Fiore & Heidemann, 2004). This effect is considered further in the Dose-response Assessment. Note that this effect is separate from the pulmonary effects of aspirated OC.

3.6 SKIN EFFECTS

Exposure of the skin to capsaicinoids results in a range of effects, including 1) an initial stinging and burning pain followed by desensitization to heat or other pain stimuli, 2) physical or structural signs of skin reactions such as erythema, wheals, or blisters and 3) allergic reactions. Data to evaluate the potential for these effects to occur are derived from human field experience, clinical testing data, and animal toxicology studies. No information was available on potential systemic effects from exposure via the dermal route.

3.6.1 Pain Responses and Desensitization to Stimuli

Busker and van Helden (1998) reviewed the toxicological implications of "pepper spray" for use by the Dutch police force. They cited several authors who have summarized impacts of volunteer exposures. Officers sprayed in the face with "pepper sprays" containing from 1 to 5% OC develop a burning pain sensation and local skin inflammation. However, the effect usually resolves within 30 min. In reports of responses compiled for greater than 2000 exposed volunteers, no cases of skin rash or blister were reported.

Recer et al. (2002) reviewed numerous studies on effects on the skin of individuals exposed to peppers or pepper extracts and concluded that effects were limited to redness (erythema) and swelling (local inflammation), but there have not been any reports of skin lesions, except those attributed to allergic responses. Stopford and Sidell (2004) reviewed several studies on the impacts of skin exposure for OC, capsaicin, and PAVA. Results of a selection of the studies cited in these reviews are presented here. Most of these studies present insufficient concentration-response data to develop quantitative estimates of pain induction thresholds. Exposure of skin to OC in the context of preparing, handling, or harvesting peppers has been reported to cause local symptoms, including prolonged burning pain, irritation, erythema (without vesiculation - blistering) (Jones et al., 1987); parethesias (numbness, tingling, or burning sensation) of the hands (Dooley & Dooley, 1996); burning pain radiating up the arm and associated with a flush response, sweating and dizziness (Weinberg, 1981). More severe reactions, including arthralgias (joint pain), fever, and skin lesions diagnosed as acute febrile neutrophilic dermatosis were reported in an individual who had picked jalapeno peppers. No cross sensitization to capsaicin was observed in a follow up patch test (Greer et al., 1993).

Similar skin reactions following application of skin creams containing capsaicin are also well documented in the medical literature, as reviewed by Stopford and Sidell (2004). Application of a 1% capsaicin solution was reported to produce a burning sensation and induce a flare response (Buck & Burks, 1986; Carpenter & Lynn, 1981). Foster and Weston (1986) also observed a flare response around the base of blisters on human skin (SE 1). According to this study, a capsaicin concentration of 0.5 μmol/L (0.5 μM, 153 μg/L, or a total dose of 0.006 μg) induced a painful reaction. Pain induction by various riot control agents was compared. At two minutes the degree of pain was comparable across the agents tested, but immediately after application pain was rated as greater for 50 μM PAVA[19] than 0.5 μM capsaicin (relative potency of equal concentrations of these two agents was not presented).

No information was available on potential systemic effects from exposure via the dermal route. However, quantitative data on skin absorption can both provide information on the potential for skin effects, and on the potential for systemic effects from skin exposure.

[19] The authors referred to this compound as n-nonanoylvanillylamine. No such name was found in standard lists of synonyms for chemical names (Toxnet, ChemIDplus), but this compound is presumed to be PAVA, because PAVA is often abbreviated as VAN, and because a synonym for PAVA is n-nonanoylvanillylamide.

Pershing et al. (2004) conducted human skin patch test studies in groups of 12 volunteers to assess the percutaneous absorption kinetics of capsaicinoid mixtures in three different solvents. Solutions containing 3% capsaicinoids (55% capsaicin, 35% dihydrocapsaicin, 10% other analogs) in mineral oil, propylene glycol, or isopropyl alcohol were administered at a total dose of 150 μg capsaicinoids per sample to the forearm of test subjects for various time periods up to 15 min. The author noted that this dosing regimen (150 μg capsaicin for 15 min) was the maximum dose tolerable to the study subjects. The results of the kinetic experiments indicated rapid uptake of capsaicin (detectable levels observed within 1 minute and time to maximum concentration in the stratum corneum occurring within 15 min). Uptake was greater in isopropyl alcohol than the other two solvents. Half-life in the stratum corneum ranged from 16 to 26 h among the capsaicinoids and solvent combinations, although the authors noted that the protocol used would limit accurate determination of half-lives greater than 24 h. In another comparative *in vitro* study that used human and rat skin, the steady state flux rate for PAVA was 0.56 μg/cm^2/h in human skin (results varied somewhat based on receptor fluid, this result was for phosphate buffered saline plus 0.5% bovine serum albumin) (Kasting et al., 1997). The results suggested that rat skin is not a reliable indicator of human skin permeability. Other studies of percutaneous absorption of PAVA (reviewed by the COT, 2002) were conducted using either an oily base or a cream, and so are less relevant to the absorption of PAVA from a spray.

Green (1996) evaluated the relative pain sensitivity of different portions of the body by comparing sensory irritation responses (measured using a psychophysical method) for capsaicin applied to the forearm versus the cheek of 20 human subjects. A range of concentrations were used to identify irritation thresholds. For the cheek, concentrations ranging from 0.33 to 33.0 μM (dissolved in ethanol) were used and for the forearm concentrations ranging from 0.003 to 10.6 mM were used. For each test, 150 μL of the test solution was applied via a 4.25 cm filter paper disk. The material was applied for 3 min by pressing the paper disk to the skin and after each minute of contact the subject was asked to rate the sensation using a defined scale (labeled magnitude scale) that has a numeric range from 0 to 94 with a series of descriptors ranging in intensity from barely detectable to strongest imaginable. In addition, the "sensation quality" was selected from a series of descriptors such as burning, stinging, itching, etc. Subjects were exposed to increasing concentrations until they reported a "strong sensation," or the highest dose was reached. These results show that the threshold for irritation was significantly higher for the forearm than for the face (Figure 3). The geometric mean response threshold for the forearm was 2.067 mM and was 0.02 mM for the face. The results indicate that the face was much more sensitive (average threshold for the forearm was 2.02 log units greater than the face). The degree of variability in thresholds was also large, covering 1.77 log units for the forearm, but only 0.67 log units for the face. This study identifies lower and upper bound estimates for skin pain induction, a SE 1 effect, of 0.007 mM and 0.03 mM, respectively (0.002 and 0.009 mg/mL, respectively). In light of this high-quality human data, no further efforts were made to identify quantitative data on skin irritation of capsaicin in animal models.

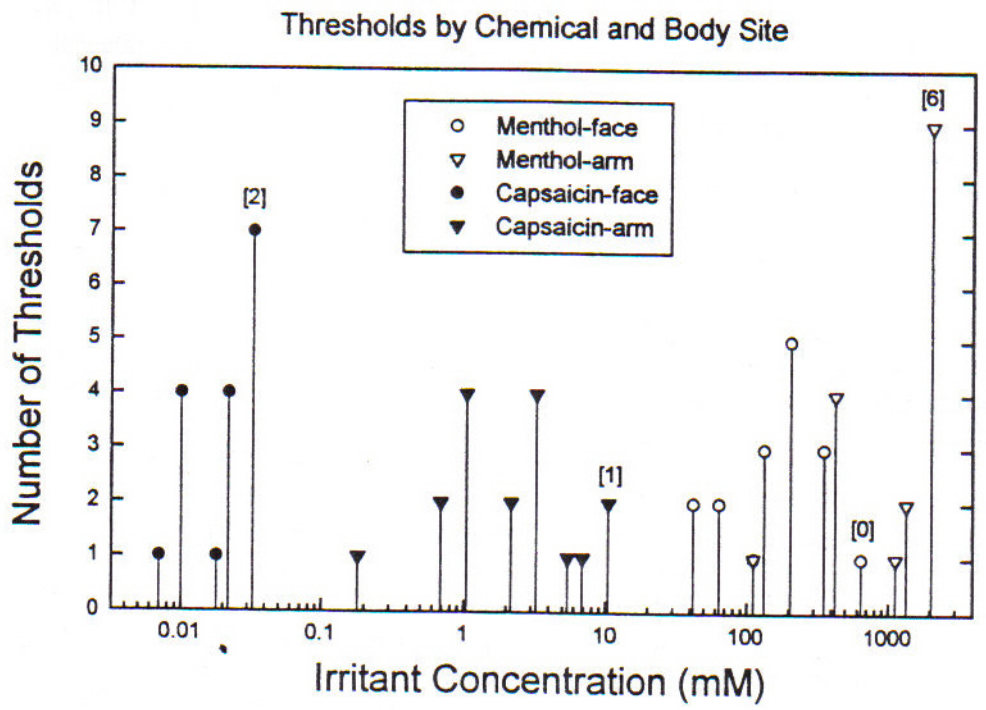

Figure 3. Thresholds for Skin Irritation (Green, 1996).

The number of subjects with a threshold at each concentration is shown by the height of each line. The number in brackets refers to the number of subjects who failed to report a criterion level of sensation at the highest concentration tested for a given chemical and site.

A solution of 3.2% PAVA (v/v) in polyethylene glycol (PEG) was used in a skin irritancy test in rabbits using an occlusive dressing and a 4-h exposure (Lett, 1996a). A 1-mL volume was tested. The rabbits were also tested on the opposite side of their body with a 48-h exposure to the same PAVA concentration after scarifying with a needle. No reaction of any type was reported at observation times of 24, 48, and 72 h. Based on these data and the reported observations in humans, either the PEG attenuated the irritant effect, the 24-h observation time was too late to observe any effect, or the rabbit is not a good model for the skin irritating effect of PAVA. In an irritation study using a hen egg model, PAVA was classified as causing medium irritation of mucous membranes (Lett, 1996b). In a review of the results of these human experience and animal testing data Weyers (1996) concluded that long-term skin or respiratory effects would not be expected in an adult exposed via the unclothed skin with 32 mg of PAVA, although a burning sensation and irritation would be expected, particularly in the mouth and mucous membranes. Particular concern was noted for children based on potential for greater ease of skin penetration (no data provided) and potential injury resulting from efforts in trying to eliminate the burning sensation.

The pharmacology literature provides data on human skin responses to topically applied capsaicin and synthetic derivatives. Exposure of skin to capsaicinoids results in vasodilatation and the resulting increased cutaneous blood flow increases the skin temperature and causes skin reddening (erythema). While this effect itself is not

clinically significant, it is a measurable physiological skin reaction that may have application for evaluating relative potency of various capsaicinoids. Simone and Ochoa (1991) measured skin responsiveness to various stimuli following repeated topical application of a cream containing 0.075% capsaicin to a 4 cm^2 area of the forearm of volunteers 4 times per day for 6 weeks. All subjects reported mild burning early in the treatment regimen, which diminished over the course of several weeks. Heat pain thresholds increased by 3.5°C over the study period (reflecting a desensitization response), but there was no affect on sensation thresholds induced by cold or mechanical impact. Capsaicin did not effect itch sensation following intradermal injection of histamine, but the resulting neurogenic vasodilatation (flare) was decreased. Fang et al. (1997) compared skin effects of capsaicin and PAVA applied to the skin in gel base at a concentration of 0.075%. In this study PAVA was not as potent as capsaicin in producing reddening and irritation of the skin (as measured by Laser Doppler Flowmetry); a finding the authors suggested supports earlier work done in rats. In a more recent study by these same authors (Fang et al., 2001), capsaicin and PAVA were found to enhance percutaneous absorption of indomethacin in nude mice, but had no adverse effect on skin structure.

Aicher et al. (2004) summarized several clinical studies that demonstrated the potential for topically applied PAVA (which is contained in product concentrations of 0.4% to 0.6%) to increase local vasodilatation responses (increased cutaneous blood flow, erythema, and increased skin temperature). No data on the degree or severity of pain experienced by test subjects was provided in most of these reports and applied doses were not given in the review. Pershing et al. (2006) measured erythematic responses in human subjects exposed over a 1.3 cm diameter area of the forearm skin for 10 min to a 5 μL aliquot of various commercial OC products (mean concentrations of total capsaicinoids ranged from 2.1 to 40 μg/μl). Degree of reddening was compared to capsaicin content of the various products and was generally dose-responsive, although the dose-response and relative effect of various capsaicinoids varied based on the metric that was used. Asian subjects had a lesser erythemic response than Caucasian subjects, suggesting there may be a genetic basis for the skin response. For capsaicinoids delivered in an alcohol base, genetic differences in alcohol metabolism may also affect the response, due to an interaction between ethanol and the “vanilloid” receptor (Trevisani et al., 2002; L. Pershing, personal communication, July 28, 2004). This hypothesis is supported by a study comparing PAVA and capsaicin in hydrogels and creams, which found a moderate correlation between *in vitro* skin permeability and *in vivo* erythema response (Wang et al., 2001). For a given concentration in a hydrogel, PAVA tended to cause a higher level of erythema in the tested Chinese subjects.

Ind et al. (undated) conducted double-blind skin-prick testing with various concentrations of PAVA and capsaicin. Capsaicin and PAVA both produced a wheal, but the size of the wheal was dose-related only for PAVA. The response for both chemicals was smaller than to the tested amount of histamine (6 mg/mL). Flare and pain resolved within 90 s, while the wheal, flare response and itching lasted for about 5 min with histamine.

As discussed in the section on neurological effects, desensitization of neural responses followed treatment of newborn animals. In addition to loss of sensory responses, Maggi et al. (1987) showed that normal tissue repair processes in the skin

may also be perturbed based on the observation that spontaneous or grooming-induced skin injuries were not repaired in rats treated with capsaicin as newborns. Similarly, marked desensitization of exposed people may lead to increased risk of injury due to the absence of adequate nociceptive feedback.

All of the available quantitative studies on skin irritation from capsaicinoids were conducted on intact skin. Capsaicinoids cause much more pain when applied to abraded skin, such as might occur in a confrontation with police. However, no information was available to quantify this difference.

3.6.2 Ethanol

Ethanol can be irritating to the skin, and can dehydrate skin following prolonged exposure. A concentration of 70% did no damage after a brief exposure, but was irritating after longer (undefined) exposures. Ethanol can also increase the degree of injury when applied to open wounds. However, the skin irritation from contact with the ethanol in the PAVA stream would be far less than the irritation resulting from the PAVA itself. No information was located indicating that ethanol causes substantial potentiation of skin irritation by other chemicals. Percutaneous absorption of ethanol is described as negligible (HSDB, 2005). At blood concentrations of 20-99 mg/dL, ethanol can cause decreased sensitivity to pain, including local skin pain. However, as described in Section 3.6.6, the systemic dose from a PAVA spray would be far too low to result in decreased sensitivity secondary to its neurological effects.

3.6.3 Allergic Reactions and Hypersensitivity

A review of occupational exposures to OC, including effects on the skin of workers handling chili peppers, did not report any cases of sensitization (Stopford, 2004). This absence of cases is supported by Chan et al. (1990), who conducted a study of 61 spice grinders, and found that 67% reported a warm or burning sensation in the skin, but no evidence of allergic disease or asthma. In their toxicological review, Recer et al. (2002) concluded that OC induces redness and swelling, but not other skin lesions. This review noted that skin blistering was reported in two cases of skin exposure to chilies or chili extract, but the blistering was associated with a delayed allergic reaction rather than an immediate direct effect. Recer et al. (2002) further reviewed four case studies of potential allergic responses and concluded, based on skin patch tests for chili extracts or capsaicin, that 3 of the 4 case reports were negative. In the one positive result (Raccagni et al., 1995) extract constituents other than capsaicin may have been responsible. However, in another study reviewed by Stopford and Sidell (2004), but not by Recer et al. (2002), capsaicin was confirmed as a contributing factor in the sensitization response. The patient developed allergic contact dermatitis after applying a 0.5% capsaicin cream, verified by patch tests to both the cream and 0.5% capsaicin in an alternative matrix (Petrolatum) (Meneghini & Angelini, 1979). No other case reports of an allergic reaction to capsaicin per se were identified.

Allergic dermatitis has been observed through a “cross sensitization” reaction (e.g., to latex), as reported by Gallo et al. (1997). However, this appears to be due to other pepper proteins in the OC extract, and not to the capsaicinoids themselves (Gallo et al., 1997). In human volunteer studies, capsaicin pretreatment worsened

inflammatory reactions induced by several immunogenic and nonimmunogenic agents (Wallengren & Moller, 1986). A similar result was seen for increased response in capsaicin pretreated guinea pigs sensitized to dinitrochlorobenzene (Wallengren et al., 1991).

The only information regarding respiratory sensitization to OC identified in the available literature was a report by Smith and Stopford (1999) of two cases among a database of 6000 officers exposed during training exercises. This study tended to report more severe effects than other studies for a variety of endpoints. The reason for this is not clear, but may have been due to a more potent batch of OC and reflected sensitization to pepper proteins.

Animal data on the sensitization potential of capsaicin are limited. One proprietary study using the Buehler method of skin sensitization by an animal repellant containing capsaicinoids was obtained (Cerven, 1993). Guinea pigs were exposed to undiluted test material in both the induction and challenge phases, and the degree of redness (erythema) and swelling (edema) was reported. There was no evidence of sensitization, but there was also no evidence of irritation in the induction phase. The use of this study is also limited by the absence of information on the percent capsaicinoids in the repellant, or on other components.

Overall the data are mostly negative for direct allergenic potential of capsaicinoids. The sporadic reports of allergic skin reactions present no consistent picture, but supportive data indicate that these reactions are likely due to other components of pepper extracts, which have been shown to cross-react with latex. The absence of widespread reporting of allergic reactions in workers who handle pepper products or in consumers who use capsaicin-based pain creams suggests that these compounds are not potent allergens. Therefore, this effect is not considered of sufficient concern to include in the dose-response assessment.

Information on skin sensitization by PAVA is based on extensive experience in over-the-counter medications, and limited animal testing. PAVA was tested in a local lymph node assay (LLNA) in CBA/Ca mice, in a standard test for sensitization potential (Donald, 2003). Concentrations of 0.8 – 4.1% were tested, based on application of 25 μL to the ear for 3 consecutive days. Although the results were negative, no conclusive result is possible, due to several study deficiencies. A comparison was made with positive controls, but there was no concurrent positive control to assure the sensitivity of the study. In addition, although there were some minimal clinical signs of toxicity (partially closed eyes, salivation, and subdued behavior at the high dose), no irritation was observed, and comparison of systemic doses with those used in the micronucleus assay (Innes & Hart, 2002) indicates that higher doses could have been tested. The issue of study sensitivity and adequacy of testing is particularly important in evaluating this study in light of the small dose-related trend seen for the stimulation index.

Lack of significant reporting of allergic skin reactions in over-the-counter pain creams containing PAVA (typically at 0.4%) supports the data for other capsaicinoids and the animal testing data for PAVA. These data are limited, however, by the absence of a systematic approach for collecting data on sensitization events from over-the-counter use. While strong sensitization events are likely to have been reported, small or borderline responses may have simply resulted in discontinuation of use. Nonetheless, concern about sensitization is low, based on the absence of positive findings in the

LLNA and reports from over-the counter use, and based on the generally negative findings on sensitization for capsaicinoids. No evidence for respiratory sensitization to PAVA was identified based on the limited use data.

3.6.4 Sources of Variability in Skin Responses

The identification of potential skin responses needs to consider potential data gaps and limitations in interpretation of existing data based on sources of variability in responses. Several factors affect the degree of exposure. For example, humidity in the air and temperature affect skin hydration, and therefore percutaneous absorption. Furthermore, weather conditions affect transport of the spray to the target and droplet size characteristics of the aerosol. Clearly, the effects observed are also influenced by clothing, which can affect exposure by shielding skin from exposure, or by prolonging exposure if the clothing is saturated with the spray. The impact of these factors on differential responsiveness to a given dose is noted in this section. These considerations include differences in response due to location on the skin surface, differences in the condition of the skin, age-related differences in skin that may impact responsiveness, and potential genetic factors affecting irritant responses. However, these issues are not addressed further in the Exposure Assessment (Section 5), since the skin is not a target organ for OC or PAVA devices.

The impact of capsaicin-responsive nerve density across the different parts of the body may affect responsiveness. Most clinical studies of effects of capsaicinoids are conducted on the forearm, presumably due to the ease of access and coverage by clothing, and minimal psychosociological impact of any effects. However, there is likely to be a wide range of variability in the response of different portions of the body, based on density of capsaicin-sensitive nerve fibers, and based on differences in skin permeability. Areas of particular sensitivity to irritants include the genitals and under the arms. Of particular importance to this assessment is the face, since it is the intended target site of the material in its use in incapacitating a belligerent. For this reason, differences in sensitivity of the face and forearm, to capsaicin induced pain responses, are important in applying clinical test data to assessment of effects in the field. As described above, Green (1996) reported that pain sensitivity was much greater for the exposed cheek than the forearm and interindividual variability was significant.

No empirical findings were obtained to quantify age-based or skin-type differences in response. Based on general toxicological principles, factors that affect barriers to skin penetration of capsaicinoids would affect responsiveness. Weyers (1996) suggested that children might be more prone to cause slight local injuries in trying to remove the burning sensation. Responsiveness may also be affected by other factors that impair the skin barrier (e.g., abraded skin, such as might occur in a physical confrontation with law enforcement officers) or by the carrier solvent (e.g., as shown by Pershing et al., 2004). Genetic differences in response have also been demonstrated in controlled human volunteer studies of Caucasian versus Asian responsiveness (Pershing et al., 2004). Skin concentrations that caused only mild irritation and erythema in most people caused a severe reaction with edema and blistering in one case with a rare combination of polymorphisms (L. Pershing, personal communication, July 28, 2004). Similarly the reported lack of effectiveness for “pepper spray” use in Thailand (E. Bauer, personal communication, July 27, 2004) may reflect genetic

variability, or it may reflect desensitization due to the high dietary capsaicinoid intake in that culture.

3.6.5 Conclusions on Skin Effects

Most of the available data are not adequate to develop a concentration-response for skin pain effects, since concentrations applied in current tests are all above the response threshold. However, the results of Green (1996) can be used to estimate thresholds and concentration-response for skin pain induction. In addition, an alternative approach considered for assessing the concentration-response was to use data for percutaneous absorption kinetics and target receptor kinetic parameters to estimate effect thresholds for skin application. However, it may not be useful to refine these estimates because (1) extensive field experience suggests that concentrations of capsaicinoids used in these applications are likely to greatly exceed the thresholds for irritation, (2) irritation is a SE 1 response but is not being tracked as an indicator response for effectiveness, and (3) the value of such an estimate may be limited for tracking a SE 1 response. As an alternative, it may be useful to assume that any "significant" contact of capsaicinoids with the skin (functionally defined by direct impact of the spray or fog) will induce a pain effect. This latter approach was used in the remainder of this HERC. Data are lacking regarding systemic effects of capsaicinoids following exposure via the skin.

3.7 OTHER EFFECTS

3.7.1 Lethality Data

Guinea pigs have been reported as the most susceptible species to the lethal effects of capsaicin, with an LD_{50} of 1.10 mg/kg; hamsters and rabbits were less susceptible (HSDB, 2005). The probable cause of death was reported as respiratory paralysis. While additional LD_{50} and LC_{50} data were located for formulated animal repellants containing capsaicins, the studies did not provide sufficient data on the percent capsaicinoids of the repellant, or on other components. Therefore, these proprietary data can not be used quantitatively, and are not presented here.

3.7.2 Reproductive and Developmental Effects

3.7.2.1 OC and Capsaicin

No studies of developmental effects of oral, inhalation or dermal exposure to capsaicin or OC were located, and no studies of OC by other routes were located. A number of studies have been conducted in which exposure to capsaicin was via injection. These studies show that a single dose to newborn rats can cause complete degeneration of sensory nerve fibers responsive to substance P, presumably due to overstimulation of nerve endings. This results in lifetime desensitization due to permanent loss of pain receptors (reviewed by Recer et al., 2002; Holzer, 1992; Olajos & Salem, 2001). Secondary developmental effects were noted in these studies, an observation the authors suggested identifies a role of sensory nervous system tissues in

normal development. A single subcutaneous dose of 50 mg/kg can cause complete degeneration, while an injection dose of 5 mg/kg causes some nerve destruction. Histopathology analyses of rats injected subcutaneously 48 h after birth showed a decreased number of unmyelinated fibers at the lowest dose tested (12.5 mg/kg), with virtually complete depletion of unmyelinated fibers at 50 mg/kg or greater. No studies looked at lower doses in an attempt to establish a NOAEL for the cytotoxic effects of capsaicin on nerves. Nerve degeneration is also observed in adult animals, but neonates are much more sensitive, with more extensive nerve degeneration; some groups of fibers are affected only in neonates. Based on analogy to the PAVA data discussed below, it appears that general developmental effects of capsaicin or OC are unlikely to be of concern, and that the only developmental endpoint of concern is the neurodevelopmental one. This latter issue is a key uncertainty for evaluating the developmental toxicity of capsaicinoids.

No reproductive toxicity studies of OC or capsaicin were identified, although as noted below for PAVA, development of reproductive function may be a concern.

3.7.2.2 PAVA

One study was located in which PAVA was tested using a standard developmental toxicity testing protocol. Knox and McKenzie (2003) treated groups of 25 time-mated Sprague-Dawley Crl:CD rats by gavage with 0, 100, 500, or 1000 mg/kg/day of PAVA in 1% carboxymethyl cellulose on gestation days 5-19. No chemical-associated maternal toxicity was observed at any dose, but the test was adequate for assessing developmental toxicity, because it was conducted up to the limit dose of 1000 mg/kg/day. Fetal weight exhibited a statistically significant decrease of 8.3% at the high dose. There was no effect on fetal or embryonic viability, sex-ratio, or visceral or skeletal abnormalities. Although this study provides reliable evidence that PAVA does not affect viability or cause malformations, neurodevelopmental toxicity was not evaluated. In addition, specialized tests to evaluate cytotoxicity to unmyelinated C fibers were not conducted. Injection studies (Hayes et al., 1984) on PAVA, as well as those described above for capsaicin, show that injection of weanlings with doses much lower than those tested in the developmental toxicity study can result in long-term effects, including hypothermia and increased nociceptive pressure threshold. As discussed for OC, these data are useful for identifying potential effects, but studies via oral, inhalation or dermal exposure are needed to determine the relevance and threshold for such effects. Based on these data, effects on viability or malformations are not a concern, but more information is needed on the potential for neurodevelopmental effects from exposure to PAVA via relevant exposure routes. Due to this lack of data, neurodevelopmental studies were not evaluated in the dose-response assessment.

No standard reproductive toxicity studies of PAVA were located. In the only available report (Traurig et al., 1984), neonatal rats were injected subcutaneously with 50 mg/kg PAVA. Sexual development was retarded, fertility was reduced, and growth was retarded throughout adulthood. This study is not adequate to evaluate the potential reproductive effects of PAVA, but indicates that reproductive and developmental toxicity is another area needing further study.

3.7.2.3 Ethanol

Ethanol is a known developmental toxicant, and is on the California Proposition 65 list for developmental effects (CalEPA, 2005). At the most severe end, fetal alcohol syndrome (FAS) is a well-known syndrome resulting from high levels of ethanol consumption during pregnancy. It is characterized by prenatal and/or postnatal growth restriction, characteristic facial abnormalities, and central nervous system effects, such as developmental delays and learning disabilities. All three sets of traits must be present for the diagnosis of FAS. When some, but not all, FAS traits are present, the condition is described as fetal alcohol effects. The amount of alcohol that it is safe to ingest during pregnancy, and the amount that is expected to cause birth defects, is somewhat controversial. However, current guidance indicates that the equivalent of about one drink per day is safe, and it is clear that the risk increases with increasing amounts of alcohol ingested. For example, the Royal College of Obstetricians and Gynaecologists states "There is an increasing body of evidence suggesting harm to the fetus from alcohol consumption during pregnancy. While the safest approach may be to avoid any alcohol intake during pregnancy, it remains the case that there is no evidence of harm from low levels of alcohol consumption, defined as no more than one or two units of alcohol once or twice a week" (RCOG, 2006, p. 1). Note that the British standard drink is smaller than the American standard drink, and corresponds to ingestion of about 8 g of ethanol. Birth defects resulting from alcohol ingestion would be SE 3 effects, since they are generally irreversible in the absence of treatment. However, the dose resulting from use in the PAVA device would be far below a dose of concern based on current guidance on alcohol consumption during pregnancy.

The available data indicate that ethanol does not cause significant reproductive toxicity (HSDB, 2005). NTP (1985) found reduced sperm motility at ethanol concentrations in drinking water that caused decreased water consumption. It is not clear if this effect was secondary to dehydration, but it occurred only at doses well above those that could occur from field use of PAVA spray.

3.7.3 Gastrointestinal (GI) Effects

3.7.3.1 Capsaicinoids

No studies evaluating GI tract effects were identified for PAVA. Ingestion of OC (in the context of natural pepper products, such as chili peppers) or capsaicin has been associated with gastrointestinal tract effects including, burning sensations, vomiting, diarrhea, and GI tract hemorrhages of varying severity (in some cases accompanied by overt bleeding). These effects can be categorized as SE 1-2, and are presumed to be relevant for all the active OC-related products (OC, capsaicin and PAVA), although most of the data has been compiled for peppers or capsaicin.

The less severe gastrointestinal tract effects of these compounds are familiar to most people who have consumed pepper products in their diet. However, this general experience is complemented by clinical studies or case reports in humans that provide quantitative estimates of capsaicin intake associated with symptoms of gastric irritation. Case studies documenting these effects have been summarized in a recent review (Stopford & Sidell, 2004). Desai et al. (1976) reported increased DNA content in gastric

aspirate (as a marker for GI tract epithelial damage) in human volunteers following intragastric infusion of 10 mg/h capsaicin, but not at 7.5 mg/h capsaicin. Increased gastric cell exfoliation was observed by Myers et al. (1987) in volunteers who ate meals containing 0.1 to 1.5 g of red pepper (capsaicin content was not provided in the review). In this study one of the subjects displayed visible gastric bleeding. In another study, 10 g/100 mL (test material not specified) administered on an empty stomach caused edema and overt bleeding, and 1 g/100 mL caused edema and bleeding (DiBartolomeis et al., 1993). In a group of 20 human volunteers given a solution containing 3% capsicum intragastrically (volume administered not presented in the review), redness, edema, and hemorrhagic spots were reported within 2 min. The incidence of symptoms was seven symptomatic subjects, four subjects with hemorrhagic spots, and one subject with a progressive hemorrhage and hematemesis (vomiting of blood) (Viranuvatti et al., 1972). Symptoms of GI tract irritation were reported in a case study of child abuse where children were disciplined by placing a cut jalapeno pepper or tobasco sauce on their tongues for 15 to 20 min. Symptoms included burning of the mouth, throat, stomach, and in some cases burning of the anus, vomiting and diarrhea (Tominack & Spyker, 1987). Two studies found that ingestion of capsicum was associated with increased acid secretion in the stomach (Myers et al., 1987; Ketusinh et al., 1966).

In addition to the above findings of human clinical observations from dietary exposure to capsaicinoids and in controlled studies, there are documented reports of the effects on individuals who have been exposed to OC in the context of civil disturbances. Thus, in an analysis of 1,531 exposures to OC sprays reported to the Texas Poison Center Network over the period 1998-2002 (Forrester & Stanley, 2003) ingestion was a route of exposure in 205 (19.9%), with half of these occurring in children aged 6 years or younger. The most common symptoms were irritation of the mouth and throat, and nausea. Another analysis (Ballantyne, 2005) involving 108 individuals who were exposed to OC sprays over a short period (about 15 min) in a civil disturbance showed the following incidence of alimentary tract symptoms: throat irritation 89%, nausea 48%, vomiting 28%. There were no hospitalizations of individuals in this group. These findings indicate that the incidence of symptoms referable to the swallowing of OC from spray devices, which produce a mist of the material, can be moderately high. However, these effects are those anticipated from swallowing any peripheral sensory irritant material, and do not lead to any significant complications or long-term health effects. Thus, they are SE 1-2 effects.

Together, these studies demonstrate that capsaicinoids (OC in peppers or capsaicin itself) can generate severe GI tract irritation, with moderately severe symptoms when sufficiently high doses are consumed. None of these studies as summarized from available reviews provide sufficient dose-response information to identify thresholds for moderately severe irritation responses (e.g., hemorrhage). However, based on the limited data, doses in the low milligram range appear capable of inducing some SE 1 effects on GI tract epithelium (e.g., burning sensation, increased epithelial sloughing). However, these doses are well within the range of normal daily intake, since adults may consume <0.1-10 mg/kg (<7 – 700 mg for a 70 kg adult) of capsaicin on days where intake occurs, by eating a spicy meal. (Since this is a direct contact effect, the appropriate dose measure is mg, rather than mg/kg.) The basis for this calculation is provided in Appendix I. Indeed, Stopford and Sidell (2004) noted that

chili pepper consumption as part of a meal can cause gastric cell exfoliation and mucosal microbleeding, with the severity at the higher doses of hot peppers comparable to that seen from ingestion of 655 mg aspirin. The bleeding was generally described as microbleeding, although one subject had grossly visible gastric bleeding after both red pepper and black pepper administration. Doses in the low gram range may induce moderately severe effects (SE 2 effects such as hemorrhage with bleeding). Insufficient information is available to determine whether children are more sensitive to the GI effects of capsaicinoids.

While the quantitative information on GI effects of capsaicin ingested as part of a spicy meal are of interest, use of such data is limited by differences between such exposure and that from swallowing OC under field use. For example, the local concentration from field use of OC may be higher than that from ingesting a comparable amount in food. In addition, food in the GI tract may moderate the effects of OC from a spicy meal.

Quantitative extrapolation from data on systemic effects of ingested OC in spicy food to potential systemic effects from field use of OC is also limited. Ingested OC undergoes first-pass metabolism, while systemic exposure from other routes would not undergo such metabolism. This means that comparable intake may result in higher tissue doses following field use exposure.

In contrast to the dietary capsaicinoid dose described above, the COT (2002) calculated that a 1 second discharge of a 0.3% PAVA spray releases 28 mg PAVA, a dose of capsaicinoid well below that in a single spicy meal. Since OC sprays are typically used at capsaicinoid concentrations of 0.2-0.6%, but may range as high as 3% capsaicinoids (Conrad, 2004), extrapolation from the PAVA data would indicate that the high end release in a single spraying incident could be as much as approximately 300 mg capsaicinoids, but is more likely to be less than 30 mg (comparable to the exposure from PAVA). These doses are in the range of the dose from a single spicy meal, with the more typical doses at the low end of the range. However, only a small fraction of the capsaicinoids discharged would usually end up in the GI tract, as discussed further in Section 5. Based on the data in Section 5, these doses may be reasonable estimates based on the high end estimates for mouth strikes, but it is likely that subjects would spit out liquid droplets striking the mouth, rather than swallowing them. The systemic dose from ocular or dermal absorption would be orders of magnitude lower. Based on these considerations, it is unlikely that enough capsaicinoid exposure could occur to induce moderate or severe GI tract effects. Results of prior case studies of OC use indicate that SE 1 effects on the gastrointestinal tract (e.g., vomiting, nausea) may occur, but these effects are not included in the dose-response assessment.

Animal studies are consistent with the human data indicating the onset of GI tract effects following oral exposure to capsaicin compounds. In the context of acute lethality studies, mice treated intragastrically exhibited necrosis with increased mucous in the GI tract. The chief and parietal cells showed pale basophilic cytoplasm and vacuolization in the low milligram dose range. In a subchronic oral study, Monsereenusorn (1983) reported that rats administered 50 mg/kg-day capsaicin via gavage for 60 days had reddened gastric mucosa with “increasing mucus materials” (p. 103). In addition to direct GI tract effects, some early studies indicated that damage to the duodenal mucosa may have secondary effects on nutrient absorption (Olajos & Salem, 2001);

however, based on several studies summarized in existing reviews, this effect has not been reported consistently. Based on the inconsistency in the data and the minimal likely physiological consequences of this secondary effect on nutrient absorption, it is not considered further in the dose-response assessment.

3.7.3.2 Ethanol

High chronic (repeated) exposure to ethanol in alcoholic drinks can cause a number of gastrointestinal effects, including irritation, and bleeding. A single acute exposure resulting in blood alcohol levels of 200-299 mg/dL can cause nausea, vomiting, gastrointestinal bleeding, and abdominal pain (HSDB, 2005). These effects are generally SE 1, although they may reach SE 2 levels at sufficiently high doses. These doses are well above those causing SE 1 central nervous system effects, and highly unlikely to occur from field use of PAVA.

3.7.4 Cardiovascular Effects

3.7.4.1 Capsaicinoids

Exposure to capsaicinoids may induce physiological reflexes affecting the cardiovascular system (Olajos & Salem, 2001). As a particular example, inhaled irritants can induce the Kratschmer reflex, which results in symptoms including apnea (cessation of breathing), bradycardia (slowed heart rate), and a biphasic fall and then rise in aortic blood pressure. Therefore there is a direct relationship between inhalation of capsaicin compounds and cardiovascular effects. However, in the several human inhalation studies where cardiovascular endpoints were measured, minimal nonclinically relevant changes in heart rate were observed, generally consisting of a 20% or smaller increase in heart rate (Chan et al., 2001; Ind et al., undated, 2001a, b). No human studies reporting a decrease in heart rate from capsaicinoid exposure were located. There was no change in heart rate in four subjects exposed to nebulized capsaicin from solutions of 2-65 μM (Collier & Fuller, 1984). In a retrospective evaluation of 81 people who came to the emergency room after exposure to OC (5% Cap-Stun spray), Watson et al. (1996) reported elevated heart rate (>100 beats/minute) in 40% and elevated respiratory rate (>20 breaths/minute) in 20% of the subjects. However, since this effect may represent factors other than the physiological effects of OC, it is difficult to use these data directly.

In the only report identified on clinically significant hypertension associated with OC use (Smith & Stopford, 1999) two cases of severe hypertension (>180/110) were reported among 6000 officers exposed to OC in training exercises. Other severe effects reported in this study included an EKG change in one patient, chest pain requiring nitroglycerin in one, and loss of consciousness (cause not available) in two. This study tended to report more severe effects than other studies for a variety of endpoints. The reason for this is not clear, but may have been due to a more potent batch of OC. Although the Kratschmer reflex refers to a fall then rise in blood pressure, and no fall in blood pressure has been observed, it is possible that the decrease was too transient to be observed by the time the subject reached the emergency room. However, based on analogy to a number of controlled studies on other sensory irritant riot control agents,

further described in Appendix D, it is likely that the observed cardiovascular changes are secondary to coughing, stress from the pain, or as a result of exertion in the confrontation). Carefully controlled and conducted studies on volunteers have shown that there are increases in both systolic and diastolic blood pressure, often with a reflex bradycardia, shortly after exposure to the peripheral sensory irritant materials 1-chloroacetophenone (CN), 2-chlorobenzylidene malononitrile (CS), and dibenz (b.f)-1,4-oxazepine (CR). In these studies, increases in blood pressure were first measured within a minute or so following irritant drenches and were moderate to marked. A direct hypertensive effect of the sensory irritants was considered unlikely based on the speed of onset, and based on a comparison of the estimated systemic dose with the injected dose needed to cause changes in blood pressure. A cold pressor response from the drenching may have contributed to the observed effect, but would have resolved rapidly. Instead, the changes in blood pressure were considered secondary to the pain, and would be likely to occur as transient effects of exposure to capsaicinoids. Cardiovascular changes have also been reported following intravenous dosing with PAVA or other capsaicinoids in animal studies. While these studies provide dose-response information on cardiovascular impacts of direct systemic administration, the data are less relevant for this evaluation than those of the human exposure studies. Therefore the animal data, while identifying potential cardiovascular impacts of capsaicin compounds reaching the systemic circulation, are not used to support a quantitative dose-response. A brief summary of these studies is provided below.

Intravenous administration of capsaicin caused a transient rise in mean systemic blood pressure (i.e., hypertension) followed by a sustained fall in dogs with no appreciable influence on the heart rate, but only caused hypotension in rabbits and guinea pigs (Toda et al., 1972; Porszasz & Szolcsanyi, 1991; 1992). In contrast, in humans, peripheral and central intravenous injection of capsaicin only caused sequential hot flushing sensations in the chest, face, rectum, and extremities but no cardiac arrhythmia or systemic hypotension was observed (Winning et al., 1986). These studies indicate that effects of capsaicin vary across the species. While the absence of a hypotensive effect of capsaicin in the Winning et al. (1986) study may be due to interspecies differences, it may also reflect the lower doses tested in humans compared to the other species. The Winning et al. (1986) study was conducted at doses up to 2 or 4 μg/kg, while the two capsaicin studies reported changes at doses of 30-100 μg/kg or higher. However, Lo et al. (1994) reported a change with PAVA at 10 μg/kg, suggesting that there may be differences in responsiveness to capsaicin and PAVA, and that the differences in dose do not explain all of the observed differences.

In animals, intravenous injection of PAVA resulted in triphasic blood pressure changes: (a) an initial reduction in blood pressure, (b) an intermediate rise, and (c) a second, more gradual fall in blood pressure (Yeh et al., 1993; Lo et al. 1994). When injected intra-arterially into the epigastric artery, PAVA caused hypotension and mild tachycardia (rapid beating of the heart) in rats (Lo et al., 1994). The triad of blood pressure changes was also observed in animals given i.v. capsaicin or its analogues (Yeh et al., 1993; Chahl & Lynch, 1987).

In summary, the findings noted above and described in more detail in Appendix D indicate that inhalation or skin contact with sensory irritants at concentrations sufficient to produce moderately severe discomfort or pain results in abrupt increases in

both systolic and diastolic blood pressure of a magnitude that may be tolerated without significant medical hazards in healthy individuals. However, as with other stressful situations, there may some individuals who may be susceptible to adverse consequences of increased blood pressure; this may include those with essential hypertension, established myocardial infarction, cardiac arrhythmias, and with diagnosed or occult aneurysms (Ballantyne, 1977; Ballantyne & Swanston, 1978; Ballantyne & Salem, 2004). Although the cardiovascular changes with OC and PAVA have not been well documented, particularly the early post-exposure effects, the fact that these materials are also peripheral sensory irritant materials and cause moderate to marked local discomfort, with associated reflexes, to the skin, eye and respiratory tract, indicates that these conclusions regarding the genesis and pathophysiological significance of cardiovascular changes will also apply to OC and PAVA.

3.7.4.2 Ethanol

"Recreational" amounts of alcohol ingestion can lead to chest pain due to coronary artery spasm or myocardial ischemia. "Modest" acute doses (above those causing mild neurological effects) can also cause atrial or ventricular arrhythmias. These effects have been reported both in subjects with underlying heart disease and in subjects with no evident heart disease, but are relatively rare. Chronic ethanol abuse can lead to myocarditis (inflammation of the muscular walls of the heart), an increased incidence of arrhythmias, stroke, and cardiac failure, while there are some reports that low chronic doses (20-30 mg/day) may decrease the risk of coronary heart disease. The cardiovascular effects of ethanol range from SE 2 (e.g., atrial arrhythmias) to SE 3 (e.g., cardiac failure, stroke). The severe cardiovascular effects of ethanol occur only after chronic exposure to systemic doses well above those that could be received from the PAVA device, as described above, while the arrhythmias are associated with acute exposure to doses well above those that could be received from such a device.

3.7.5 Thermoregulatory Effects

3.7.5.1 Capsaicinoids

Capsaicinoid compounds also affect thermoregulatory processes. For example, de Vries and Blumberg (1989) reported subcutaneous injection of 15 mg/kg capsaicin into mice produced a profound drop in body (rectal) temperature with a single exposure, but resulted in rapid desensitization of (or tolerance to) the hypothermic response. Based on the body of injection studies in animals, capsaicinoid compounds appear to impair heat escape and cause irreversible perturbations in thermoregulation (Olajos & Salem, 2001). No information on this effect with PAVA was identified, but presumably a similar effect would exist. This effect is not considered further in the dose-response assessment due to the absence of studies by a relevant route of exposure and the likely minimal adversity of the observed effect.

3.7.5.2 Ethanol

Acute ingestion of relatively small amounts of ethanol increases blood flow in the skin and stomach. This results in a feeling of increased warmth, while in reality, heat is being lost (SE 1). Consumption of large (undefined) amounts of ethanol upsets the body's temperature regulatory mechanism. Acute exposure to very high levels of ethanol (blood alcohol levels of 300-399 mg/dL) can cause hypothermia, an SE 2-3 effect. Subjects with this level of alcohol in the blood may be stuporous or comatose (SE 3). Such severe effects would occur only at systemic doses well above those that could occur following field exposure to PAVA devices.

3.7.6 Neurological Effects

3.7.6.1 Capsaicinoids

Capsaicin is a potent modifier of nociception responses, several of which are described in detail in the context of ocular, respiratory, and skin effects. In addition to these sensory nervous system affects, however, exposure at high acute doses may also cause neuromotor dysfunction and very high doses have resulted in permanent damage to the sensory nervous system, due to over-stimulation of the nerve fibers (Olajos & Salem, 2001). The primary dose-response data were described in the context of developmental toxicity, in Section 3.7.2. As described there in more detail, permanent or long-lasting desensitization of substance P-responsive sensory neurons has been reported in newborn rats given high systemic doses (e.g., via injection) of capsaicin (reviewed in Recer et al, 2002; Olajos & Salem, 2001). A distinction between two different nervous system responses can be made; desensitization (decreased response to capsaicin) and neuroinhibition (decreased response to any stimulus), where the latter response is a neurotoxic effect of capsaicin (Busker & van Helden, 1998). Only two human studies reported on potential neurological effects. In an evaluation of medical complaints among 6000 corrections officers exposed to OC in training exercises, Smith and Stopford (1999) reported that 16 patients had headache (9 described as severe). In the absence of a control group, it is not clear if the headache was exposure-related, and, if it was, whether the effect was a neurological or secondary to changes in blood pressure. This study tended to report more severe effects than other studies for a variety of endpoints. The reason for this is not clear, but may have been due to a more potent batch of OC. Dizziness was also reported in one study of the effects of occupational exposure to hot peppers (Weinberg, 1981), but the cause of the dizziness is unclear.

3.7.6.2 Ethanol

Ethanol is primarily a depressant of the central nervous system, although it may initially appear to act like a stimulant. The central nervous system is perhaps the most sensitive target of acute low-level exposure to ethanol. Because ethanol vapor is readily absorbed systemically, and inhaled ethanol does not undergo first-pass metabolism in the liver, ethanol vapor can be a more potent cause of neurological

effects than ingestion. Concentrations of 20-99 mg/dL in the blood can cause decreased visual acuity, muscular incoordination, impairment of ability to drive, mood changes, decreased sense of smell and taste, and elevated pain threshold (including the threshold for skin and eye pain). A concentration of 20-30 mg/dL has been reported to increase reaction time, decrease fine motor control, and impair judgment, and a concentration of 35 mg/dL in the blood has been reported as impairing driving. However, most state drunk-driving laws define driving under the influence (DUI) as a blood alcohol concentration of 0.08% (80 mg/dL), while a few states define it as a blood alcohol concentration of 0.1% (100 mg/dL) (OHS, 2005).

The magnitude of neurological effects increases with the concentration of ethanol in blood. Effects at 100-199 mg/dL include staggering gait and marked impairment of driving ability. Obvious intoxication occurs at 150-300 mg/dL, with more than 50% of the population showing signs of gross intoxication at 150 mg/dL. A blood concentration of approximately 400 mg/dL can result in death, although a concentration as low as 250 mg/dL has proved fatal. A concentration of 400 mg/dL corresponds to a lethal dose of 5-6 g/kg in an adult, and 3 g/kg for a child. Neurological effects of ethanol range from SE 1 to SE 3 effects. These effects are summarized in Table 5. As noted in the beginning of Section 3, the worst-case estimate of the systemic dose from spraying with PAVA is 4.2 g, or is less than 1/3 the dose from a “standard drink” in the U.S. Although ethanol absorbed from such a spray would bypass first-pass metabolism, the amount hitting the body, and the subsequent amount absorbed would be much smaller (e.g., see Chapter 5). Therefore, based on these considerations neurological effects are not considered likely effects of exposure to ethanol as a solvent in PAVA spray, and so are not considered in the dose-response assessment. The worst-case scenario also indicates that the systemic dose of ethanol would be far too low to cause decreased sensitivity to pain, and so decreased effectiveness due to the solvent is also not a concern. Chronic alcohol abuse can result in tolerance (decreased effects for a given concentration in blood). Physiological dependence can also result, resulting in withdrawal symptoms when alcohol consumption is terminated.

Table 5. Summary of Neurological Effects of Ethanol

Concentration in Blood (mg/dL)	Concentration in Blood (%)	Primary Effects	SE Level
20-30 mg/dL	0.02-0.03%	Increased reaction time, impaired judgment	1
35 mg/dL	0.035%	Impaired driving	1
20-99 mg/dL	0.02 – 0.099%	Decreased visual acuity, decreased coordination, mood changes	1
100-199 mg/dL	0.1-0.199%	Staggering gait, marked impairment of driving ability	1
150 mg/dL	0.15%	More than half of population shows signs of gross intoxication	1
150-300 mg/dL	0.15-0.3%	Obvious intoxication	1-2
400 mg/dL	0.4%	Lethal	3

3.7.7 Other Target Organ Effects (Liver and Kidney)

3.7.7.1 Capsaicinoids

No repeated dose studies were identified that evaluated systemic effects following inhalation or dermal exposure to capsaicinoids. Several repeated dose oral studies for capsaicinoids have been conducted. A 90-day dietary study in rats was conducted for PAVA (Posternak et al., 1969). The single dose tested of 10 mg/kg-day did not induce any adverse effects, although the study is limited by the single dose regimen and limited range of endpoints examined. Other repeated-dose systemic toxicity studies for OC or capsaicinoids were reviewed by Olajos and Salem (2001). Lee (1963a, b) observed hepatic necrosis in rabbits administered capsaicin (the dosing regimen was not described in the review by Olajos & Salem, 2001). Two studies (Monsereenusorn, 1983; Nopanitaya, 1973) identified clinical chemistry changes following subchronic dosing of rats. In one of these, Monsereenusorn (1983) reported that rats administered 50 mg/kg/day capsaicin via gavage for 60 days had significant decreases in several clinical chemistry parameters (plasma urea nitrogen, glucose, phospholipids, triglyceride, transaminase, alkaline phophatase). However, increases (rather than decreases) in the liver enzyme parameters would be the expected result of necrotic liver changes, and increases rather than decreases in plasma urea nitrogen would indicate impaired kidney function. Decreases in glucose and lipids could reflect impaired liver function, but these are not sensitive markers. This study did identify GI tract changes, as described above. A 4-week feeding study of ground chili in mice (Jang et al., 1992) did not identify any adverse effects; however, further information on

the dosing regimen was not described in the review by Olajos and Salem (2001). These data suggest that the NOAEL for systemic effects following oral exposure to capsaicin, PAVA, or, by extension, OC, dosing is at least 10 mg/kg/day and may be as high as or higher than 50 mg/kg /day.

Limitations in the available studies preclude developing a definitive threshold for adverse effects for these endpoints. However, a rough dose calculation shows that these effects are very unlikely from use of OC or PAVA. As noted above, a typical use of PAVA releases 28 mg, while as much as 1 g capsaicinoids may be released in an OC spray event. Assuming the entirety of these amounts hit the body and was absorbed with efficiency comparable to oral absorption, the resulting doses would be 0.4 mg/kg and 14 mg/kg, respectively, for a single event. (These very high exposure estimates are refined in the exposure section. Based on data presented there, the actual systemic dose would be orders of magnitude lower, unless a substantial volume of spray hits the mouth and is swallowed.) These dose estimates are in contrast to multiple-dose NOAELs of at least 10 mg/kg-day, and possibly higher than 50 mg/kg-day. This provides a margin of safety even using very conservative assumptions. A comparable calculation could not be made based on the fogger scenario.

3.7.7.2 Ethanol

No significant acute effects of ethanol on other organs were identified. Chronic high-level exposure can cause a number of dose-related effects on the liver, including fatty infiltration of liver, hepatitis, and cirrhosis. Fat in the liver is an early event and can occur at “relatively low doses” in normal individuals. Other effects of chronic high-level include anemia resulting from blood loss and iron deficiency; pancreatitis (inflammation of the pancreas); and decreased immune function. These chronic effects of ethanol range from SE 2 to SE 3.

3.7.8 Immunotoxicity

Only limited data are available. No studies were identified that evaluated specifically effects on immunosuppression. Capsaicinoids induce inflammatory responses as described above for the skin and respiratory tract. As discussed above (Section 3.5.2), capsaicinoids do not appear to cause skin or respiratory sensitization.

3.7.9 Cancer

3.7.9.1 OC and Capsaicinoids

Chili peppers are a common dietary exposure and investigations into potential cancer concerns have focused on oral intake. This route of exposure may differ significantly from inhalation exposure, since capsaicinoids are metabolized via multiple pathways in the liver (reviewed in Olajos & Salem, 2001), and may generate compounds that can alkylate DNA or other cellular macromolecules. First-pass metabolism in the liver is important for oral exposure, but liver metabolism would play a smaller role in exposure via other routes. Since the primary route of interest for use of

these substances in law enforcement is via skin and inhalation exposure, the dietary studies are of limited direct utility and are only described briefly.

In limited epidemiological studies, increased consumption of chilies correlates with gastric cancer within a population (thus controlling for other dietary and genetic factors) (Lopez-Carillo et al., 1994). No standard carcinogenicity bioassays were identified for OC or capsaicin. In a short-term study, capsaicin administered in the diet for 35 days resulted in duodenal adenocarcinoma in a single animal in each of three treated groups, but not in control animals or at the high dose (Toth et al., 1984). The lack of a clear dose-response and limitations in the study design precludes decisions regarding potential tumorigenicity of capsaicin in this study. In other studies capsaicin has been found to inhibit carcinogenesis of a number of chemicals, an effect that has been hypothesized to result from inhibition of the metabolism of these chemicals to an active form, by inhibiting cytochrome P450 activity (Surh et al., 1995, 1998; Teel et al., 1997; Reilly et al., 2003b).

Overall mutagenicity data for capsaicin are mostly negative. For example, capsaicin was reported as negative in Salmonella mutagenicity testing sponsored by the NTP (2004a) and in other studies (reviewed in Recer et al., 2002), but was weakly positive in some studies (Toth et al., 1984). The evidence is stronger that capsaicin and chili pepper extracts can induce chromosomal aberrations (reviewed in Recer et al., 2002). However, epidemiological studies in communities with high chili spice intakes do not support this and a report from Hazelton Europe (Marshall, 1994) commissioned by the Home Office/Department of Health in the UK did not confirm significant bone marrow effects in mice using a recognized toxicological protocol. Based on the weight of evidence it is not clear if capsaicin can induce tumors. Furthermore, whether tumors would be more likely to arise via an irritant or mutagenic effect is also uncertain. It is plausible that a direct irritation effect is at least a contributor to any tumor response, based on the site of tumors in the GI tract in the limited epidemiology and animal studies. Irritation is generally considered a tumor promoting effect, and therefore, in the absence of chronic capsaicin exposure would not be a relevant consideration for law enforcement use of capsaicin compounds. This mode of action consideration decreases the potential importance of tumors as an effect of sufficient concern to evaluate in the dose-response assessment. Overall, a carcinogenic potential of OC cannot be ruled out, but the data indicate that any such activity would be very low potency. In light of the low potency, expected low systemic exposure, mode of action considerations, and rare exposure (although this exposure may be higher for officers using a cone spray), this endpoint is not considered of sufficient concern to evaluate in the dose-response assessment.

3.7.9.2 PAVA

No human or animal data were identified that evaluated the carcinogenic potential of PAVA. PAVA has undergone testing using a battery of standard genotoxicity tests conducted according to test guidelines. It was negative with and without exogenous metabolic activation (S9) in a well-conducted bacterial mutagenicity study (Stevenson, 2001), but clearly positive ± S9 in an *in vitro* chromosome aberration assay (Murie, 2001). PAVA was also weakly positive in a mouse lymphoma mouse in the presence and absence of S9 (Riach, 2001). The resulting mutants were

predominantly small colonies, indicating that the predominant effect was the induction of large chromosomal deletions (chromosome aberrations). In *in vivo* testing, PAVA was negative in an *in vivo* unscheduled DNA synthesis (UDS) assay when tested up to doses resulting in clinical signs of toxicity (Clay, 2003). The final test conducted to address the inconsistent results was a mouse micronucleus assay (Innes & Hart, 2002). This study was negative, but confidence in the study is decreased by the varied dose-responses seen in the range-finding toxicity studies and errors in the summary tables. Nonetheless, data reported in the study are sufficient to determine that the test material reached the target at sufficiently high doses. The micronucleus was chosen as the final study type based on the approach in the U.K. However, in the U.S., it would be considered more appropriate to conduct an *in vivo* chromosome aberration study, in light of the consistent evidence for weak clastogenicity in the *in vitro* chromosome aberration and mouse lymphoma assays, as well as weak clastogenic effect of capsaicin. Overall, these data indicate that PAVA is not mutagenic, but it is weakly clastogenic. Based on the very weak response and the low systemic doses resulting from use compared to dietary exposure, this endpoint is not considered of sufficient concern to evaluate in the dose-response assessment.

3.7.9.3 Ethanol

The International Agency for Research on Cancer (IARC, 1998) concluded that "There is *sufficient evidence* for the carcinogenicity of alcoholic beverages in humans. The occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus and liver is causally related to the consumption of alcoholic beverages" (p. 8). IARC (1998) also concluded that there is inadequate evidence for the carcinogenicity of ethanol and of alcoholic beverages in experimental animals. Overall, IARC classified alcoholic beverages as "*carcinogenic to humans (Group 1)*" (1998, p. 8). A recent bioassay of ethanol in drinking water conducted by the National Toxicology Program (NTP, 2004b) was designed to evaluate the effect of the mixture of urethane and ethanol in water, and so the study design was inadequate to determine the carcinogenicity of ethanol alone in the test species (male and female mice). The study did conclude that there was "weak evidence" of an interaction of ethanol in the carcinogenicity of urethane in B6C3F1 mice. The NTP Report on Carcinogens (NTP, 2005) lists alcoholic beverage consumption as "known to be a human carcinogen." The American Council of Governmental Industrial Hygienists considers ethanol to be in category A4, not classifiable as to human carcinogenicity (ACGIH, 2001). The mechanism of ethanol carcinogenicity is not known, but may involve local cytotoxicity or genotoxicity of the acetaldehyde metabolite. The mode of action is important in a making a definitive conclusion that a single high dose exposure is not a likely cancer risk. Nevertheless, ethanol is not a potent genotoxicant and therefore, cancer risk from acute exposure is considered low. Cancer is an SE 3 effect.

3.7.10 Flammability

Use of OC based products creates aerosols of flammable solvent and the application of flammable solvents to individuals. This results in the potential for burns if the solvents are ignited by an open flame or a spark. A concern has been raised that this could occur as a result of the use of tobacco products. In addition, officers in some police departments carry both OC and a conducted energy device. Policy recommends use of the approved respective conducted energy device if the subject is not subdued by the use of OC. In such cases, there are only a few seconds between the use of OC and the follow-up by a conducted energy device. This has raised the issue of whether there is a risk of igniting the solvents and propellants in the OC spray, since usage of a conducted energy device following OC spray exposure may create an arc between the dart and the skin to carry the electric charge, and this spark has the potential for igniting highly flammable materials.

There have been a few very rare reports of such ignition in field use. A controlled test of a popular conducted energy device used immediately after spraying a dummy with PAVA in 50% ethanol:water was also able to achieve ignition. In a report published by the UK HOSDB, the findings include that "there is a significant risk of ignition if a taser is fired at a target that has been previously sprayed with either CS or PAVA incapacitant spray. CS spray is twice as likely as PAVA spray to ignite but PAVA solvent burns with a blue flame that is difficult to see in bright light conditions" (Wilkinson, 2005, p. iii). The author strongly recommends that the TASER® not be used against a subject who has already been sprayed with either CS or PAVA, when they are present with a flammable solvent (Wilkinson, 2005).

Ignition resulted in a controlled study when a dummy was struck with a TASER® and then sprayed with an OC formulation using propane as a propellant (Finley, 2005). The reverse order (spraying followed by TASER® use) was apparently not tested. In one case of ignition, the "pepper spray" was water-based, but no information on the propellant was available. The police officers hypothesized that the ignition of the target's hair resulted from something in the hair (Policeone.com, 2004). No information was available on the solvent and propellant in other case reports of ignition when OC and a conducted energy device were used together. Based on these concerns, the potential for flammability was evaluated in the HERC, based on data for lower explosive limits (LEL). Table 6 presents a summary of the lower explosive limits for the major solvents used for OC devices. The basis for these numbers is discussed in Appendix F.

Table 6. Lower Explosive Limits for Solvents

COMPOUND	Lower Explosive Limit (%)	Reference
Ethanol	3.3	http://www.carolina.com/stcms/acrobat/stc_msds/POM_MSDS/Ethanol.pdf
isopropanol	2.0	http://www.jtbaker.com/msds/englishhtml/i8840.htm
sec-butanol	1.7	http://www.jtbaker.com/msds/englishhtml/b6302.htm
propylene glycol	2.6	http://www.jtbaker.com/msds/englishhtml/p6928.htm
DPM glycol	1.1	http://www.dow.com/PublishedLiterature/dh_056c/09002f138056ced8.pdf?filepath=oxysolvents/pdfs/noreg/110-00618.pdf&fromPage=GetDoc
d-limonene	0.7	http://www.safe-react.com/msdsdlim.htm
water	NA	-

*100% solvent used in flammability analysis therefore: $\propto$ = 1.00

3.8 SUMMARY OF EFFECTS IDENTIFICATION

The intended effects of the OC/PAVA sprays are irritation and incapacitation. Ocular irritation is the primary effect, followed by respiratory and skin irritation. Unintended effects evaluated in this report include bronchospasm, pulmonary effects (hemorrhage, alveolar emphysema), aspiration and pressure injury to the eye. Many other unintended effects were considered in this evaluation, but were found to have a low health consequence, low probability of occurrence, or very limited data and were not evaluated in the Dose Response or Exposure Assessment sections of this report. Tables 7 and 8 summarize all the potential effects initially considered.

Table 7. Summary of Effects Considered for OC & PAVA.

Effects	Severity & Effectiveness Level	Overall Concern Level for Effectiveness and Risk Characterization
Ocular Effects		
Irritation (burning pain, lacrimation, redness, conjunctival inflammation, increased corneal opacity, swelling, and blepharospasm)	1	Effect of concern – Intended effect for large aerosol droplet sizes
Corneal burns and abrasion	2-3	Attributed to solvent carrier or secondary effect from rubbing eyes; addressed qualitatively
Decreased mechanical and chemical sensitivity	1	Considered a secondary effect – health effects would be secondary to decreased sensitivity
Focal epithelial damage and Punctate epithelial erosion of cornea	1	Effect of concern – reported in field case studies, but data inadequate to include in assessment
Permanent visual damage	3	Low concern – reported as a very rare event in field case studies; data inadequate to include in assessment
Increased intraocular pressure	1-3	Effect of concern for individuals with glaucoma based on analogy to other sensory irritants – data inadequate to include in assessment
Pressure injury from liquid stream	1-3	Effect of concern – limited threshold data for quantitative assessment
Respiratory Effects		
Irritation (mucous production, sneezing, burning sensation, coughing, and shortness of breath)	1	Effect of concern – Intended effect for small aerosol droplet sizes
Nasal irritation	1	Effect of concern – addressed qualitatively, because all concentrations of capsaicinoids used in these applications are likely to greatly exceed the thresholds for irritation
Bronchospasm	1- 3	Effect of concern – included in quantitative assessment based on thresholds in human clinical studies
Pulmonary effects (hemorrhage, inflammation)	2-3	Effect of concern – included in quantitative assessment based on thresholds for this and other lung histopathology in animal studies
Respiratory arrest	3	Effect of concern – data inadequate to include in quantitative assessment
Reactive Airways Dysfunction Syndrome (RADS)	1-3	Effect of concern – likely at high concentrations, based on analogy to other riot control agents, but no evidence of an effect based on OC exposure alone
Tachyphylaxis	1	Low concern – endpoint represents a decrease in effect
Aspiration	1-3	Effect of concern – included in quantitative assessment based on human fluid aspiration thresholds

Effects	Severity & Effectiveness Level	Overall Concern Level for Effectiveness and Risk Characterization
Skin Effects		
Skin pain and irritation (redness, burning sensation, inflammation, flare response)	1	Effect of concern – addressed qualitatively, assessment because all concentrations of capsaicinoids used in these applications are likely to greatly exceed the thresholds for irritation
Blister	1	Low concern – not supported at exposures relevant to field use, data inadequate to include in quantitative assessment
Desensitization (tachyphylaxis)	1	Considered a secondary effect – health effects would be secondary to decreased sensitivity
Sensitization (allergic reactions)	1-2	Low concern – not supported by the available data
Other Effects		
Reproductive and developmental effects	2-3	Effect of concern – no effects in standard developmental toxicity assay, but neonatal exposure impairs growth and development. Data inadequate to include in quantitative assessment
Gastrointestinal irritation (burning sensation, vomiting, diarrhea, hemorrhage); decreased nutrient absorption	1-2	Effect of concern – data inadequate to include in quantitative assessment
Cardiovascular (blood pressure and heart rate changes)	1-2	Effect of concern – data inadequate to include in quantitative assessment
Thermoregulatory effects (flush response, hypothermia)	1	Low concern- absence of studies by a relevant route of exposure and likely minimal adversity
Neurological symptoms (headache, dizziness)	1	Low concern- absence of adequate concentration-response data and likely minimal adversity
Paresthesia (numbness in hands),	1	Low concern – very rare event, not supported at exposures relevant to field use, data inadequate to include in quantitative assessment
Arthralgias (joint pain)	1	Low concern – very rare event, not supported at exposures relevant to field use, data inadequate to include in quantitative assessment
Neurotoxicity (neurodevelopment, neuroinhibition)	2-3	Effect of concern, particularly neurodevelopmental – data inadequate to include in assessment
Other target organ effects (liver and kidney)	1-2	Low concern – small exposure compared to those shown not to cause effects
Immunotoxicity	2	Low concern – no data to address endpoint
Cancer	3	Low concern – low potency in limited animal studies, expected low systemic exposure, and rare exposure
In-custody death	3	Low concern – weak association with OC and very low risk, multifactorial cause
Flammability	1-3	Effect of concern – included in quantitative assessment based on lower explosive limit

Table 8. Summary of Effects Considered for Ethanol in Context of PAVA Devices.

Effects	Severity & Effectiveness Level	Overall Concern Level for Effectiveness and Risk Characterization
Ocular Effects		
Irritation (burning, pain, blepharospasm, hyperemia)	1	Low concern - transient eye irritation, but this irritation would be less severe and more transient than the irritation from the PAVA itself
Respiratory Effects		
Irritation & coughing	1	Low concern - large droplet size from this device would result in minimal respiratory tract effects, quantitative data on irritation were not further explored
Skin Effects		
Skin irritation (pain, burning, drying)	1	Low concern – irritation less severe than that of the PAVA itself
Other Effects		
Developmental effects	3	Low concern – systemic dose would be far below the dose of concern based on current guidance on alcohol consumption during pregnancy
Reproductive effects (decreased sperm motility)	1-2	Low concern – seen only at very high doses, not clear if effect due to ethanol or secondary to dehydration
Gastrointestinal irritation (burning sensation, vomiting, diarrhea, hemorrhage, abdominal pain)	1-2	Low concern – seen only at near-lethal acute doses or high chronic exposure
Cardiovascular (arrhythmias, myocardial ischemia)	2-3	Low concern – effects are relatively rare, occur at doses above those likely to occur
Cardiovascular (myocarditis, cardiac failure, stroke)	2-3	Low concern – effect of chronic high doses
Thermoregulatory effects (flush response, hypothermia)	1-3	Low concern – low health concern (SE 1) or occurs only at very high doses (SE 2-3)
Neurological symptoms (decreased visual acuity, muscular incoordination, impairment of ability to drive, mood changes, decreased sense of smell and taste, elevated pain threshold, increase reaction time, decrease fine motor control, and impair judgment)	1-3	Low concern – even SE 1 effects occur at doses above those likely to occur
Other target organ effects (liver and kidney)	2-3	Low concern – effect of chronic high exposure
Cancer	3	Low concern – effect of chronic high exposure
Flammability	1-3	Of concern, included in the quantitative assessment

Table 9 lists the identified effects evaluated through the HERC process.

Table 9. Effects of Concern Evaluated in the HERC.

Effects	Severity & Effectiveness Level	Comments
Eye irritation and blepharospasm	1	Intended effect for devices delivering large aerosol droplet sizes
Pressure injury from liquid stream	1-3	Included in quantitative assessment based on threshold data from studies with pig eyes
Respiratory irritation	1	Intended effect for devices delivering small aerosol droplet sizes
Bronchospasm	1-3	Included in quantitative assessment based on thresholds in human clinical studies
Pulmonary effects (hemorrhage, inflammation)	2-3	Included in quantitative assessment based on thresholds in animal study
Aspiration	1-3	Included in quantitative assessment based on human fluid aspiration thresholds
Flammability	1-3	Included in quantitative assessment based on explosive limit

Table 10 lists the identified effects that are not evaluated through the HERC process, due to insufficient data to quantify, or because the effects are associated with a low level of concern because the effects are not associated with the capsaicinoid, the effects have a very low probability of occurrence, or the health consequence is very low.

Table 10. Identified Effects not Included in Quantitative Evaluation

Unintended Effects	Severity & Effectiveness Level	Comments
Corneal burns	3	Not associated with capsaicinoid, addressed qualitatively
Decreased mechanical and chemical sensitivity	1	Very low health consequence
Focal epithelial damage	1	Inadequate data to quantify
Corneal abrasion	2	Not associated with capsaicinoid, addressed qualitatively
Punctate epithelial erosion of cornea	1	Inadequate data to quantify
Permanent visual damage	3	Very low probability, inadequate data to quantify
Increased intraocular pressure	1-3	inadequate to quantify
Nasal irritation	1	Low health consequence; all effective concentrations are likely to exceed threshold; addressed qualitatively
Respiratory arrest	3	Inadequate data to quantify
Reactive Airways Dysfunction Syndrome (RADS)	1-3	inadequate to quantify
Tachyphylaxis	1	Very low health consequence
Skin irritation	1	Low health consequence; all effective concentrations are likely to exceed threshold; addressed qualitatively
Blister	2	Very low probability, inadequate data to quantify
Desensitization	1	Very low health consequence
Sensitization	2	Not associated with capsaicinoids
Reproductive and developmental effects	2-3	Inadequate data to quantify
GI irritation	1-2	Inadequate data to quantify
Cardiovascular and thermoregulatory effects	1-2	Inadequate data to quantify
Neurotoxicity	1-3	Inadequate data to quantify
Paresthesia	1	Very low probability, inadequate data to quantify
Arthralgias (joint pain)	1	Very low probability, inadequate data to quantify
Other target organ effects (liver and kidney)	1-2	Inadequate data to quantify; although exposures unlikely to exceed threshold for moderate or severe effects
Immunotoxicity	2	Inadequate data to quantify
Cancer	3	Very low probability
In-custody death	3	Very low probability; not associated with capsaicinoids

4 DOSE-RESPONSE ASSESSMENT

The second phase in the HERC framework is the dose-response assessment. The dose-response assessment refers to the process of evaluating information on the magnitude or intensity of dose required to produce the physiological effect(s) or the resultant behavioral response of interest. As described above, seven effects (two potentially intended and five unintended) were of sufficient concern and had adequate data to include in a quantitative dose-response assessment. The intended effects were: (1) eye irritation and blepharospasm (the intended effect for devices delivering large aerosol droplet sizes, SE 1) and (2) respiratory irritation (the intended effect for devices delivering small aerosol droplet sizes, SE 1). All of the unintended effects were potentially severe. They were: (1) pressure injury to the eye from the liquid stream (SE 1-3), (2) bronchospasm (SE 1-3), (3) pulmonary effects (SE 2-3), (4) aspiration (SE 1-3), and (5) flammability (SE 1-3).

4.1 EYE IRRITATION AND BLEPHAROSPASM

Eye irritation and blepharospasm are the intended effects for this weapon system, particularly for devices delivering large aerosol droplet sizes. Very little data were available on effect levels or thresholds for ocular effects. Because this is an intended effect, a threshold for the target would ideally identify the first concentration that would cause a very high level (e.g., 90%) response. Concentration-response data would also be desirable for considering effects to the user or bystander, but in the absence of such data, the desired threshold for effects on these groups would be the eye irritation threshold. The only available effects data were for concentrations above both thresholds. These were violent pain after capsaicin instillation in the rat eye at 50 μg/L (Jancso et al., 1968), and an EC_{50} in the guinea pig blink test of 46 μg/L reported for PAVA by Battensby et al. (1981). Because a high response is desired for the intended effect, a concentration of 50 μg/L is used as the threshold for a high level of effectiveness.

Conversely, the concentration of 50 μg/L is well above the threshold for eye irritation. Although a factor of 10 is typically used to extrapolate from an effect level to an effect threshold, a larger factor is needed here, because of the severity of the effect. Therefore, a factor of 10 is used to account for the severity of the effect at this concentration, and another factor of 10 is used as an estimate of the no effect level for irritation. No additional factor for extrapolation from animals to humans is used, since this is a direct contact effect for which rat and human physiology appears to be similar. Therefore, an estimate of the eye irritation threshold is 0.5 μg/L. However, in light of the considerable uncertainty regarding extrapolation to this threshold, it is prudent to assume that any significant eye contact with capsaicinoids will be irritating.

Eye irritation and blepharospasm can result from the ethanol solvent, although with much lower potency than PAVA or OC. The most relevant data are that a splash of an alcoholic drink containing 40-50% ethanol causes immediate “smarting,” but only superficial injury to the human eye. No information was located about interactions with other eye irritants. Because irritation and blepharospasm from the ethanol in the PAVA delivery stream would be less severe and more transient than the irritation from the

PAVA itself, the presence of the ethanol solvent does not alter the overall dose-response conclusion for eye effects – which it is prudent to assume that any significant eye contact will be irritating and cause blepharospasm.

4.2 RESPIRATORY EFFECTS

4.2.1 Estimation of Dose to the Regions of the Respiratory Tract

Table 5 in Section 3 summarized effect levels identified in the various respiratory studies with capsaicin, OC, or PAVA. Three respiratory effects are of interest: respiratory irritation, bronchoconstriction, and pulmonary effects (protection from hemorrhage and alveolar emphysema). The deposition region for the latter two endpoints is obvious. Pulmonary effects were calculated based on the dose deposited to the pulmonary region, and bronchoconstriction was calculated based on the dose deposited to the tracheobronchial region. However, the definition and target region for cough (as a surrogate for incapacitating respiratory irritation) is less clear. Based on the available data, this endpoint was defined as capsaicin-induced cough in a high percentage of tested subjects, as a surrogate for cough in a high percentage of all exposed subjects. As described in Section 3, cough appears to result from stimulation of the C fibers in both the head and tracheobronchial regions of the respiratory tract. This makes it more complicated to calculate the dose of interest. This assessment assumes that cough is related to the tracheobronchial dose for consistency in comparison with the doses causing bronchoconstriction. As documented in Appendix E and Table 3, the head and tracheobronchial doses were very close (differing by <10%) for most studies and exposure conditions. Larger differences were seen under conditions of deeper inhalation and tighter aerosol droplet size distributions.

To facilitate comparison across studies, the various dose units reported by different studies were converted to consistent units, as described further in Appendix E. While a number of assumptions were involved in calculating the deposited dose for some of the studies, particularly in the absence of complete documentation (e.g., flow from the nebulizer, particle size distributions, and depth of breathing), this approach does allow for an order-of-magnitude estimate of the dose, to facilitate comparisons with calculations of deposited dose in Section 5. The inhaled concentration of capsaicin was converted to dose deposited to the tracheobronchial and pulmonary regions. Study-specific aerosol droplet size information was used to determine the deposition fraction for each study. In the absence of study-specific information, an aerosol droplet size (mass median aerodynamic diameter, or MMAD) of 3 μm and a geometric standard deviation of 3 μm was assumed for nebulizer studies, resulting in a tracheobronchial deposition fraction of 0.22 and a pulmonary deposition fraction of 0.18. Deposited doses were not calculated for the occupational studies of dust exposure, due to the large uncertainty about particle size of the dust. Based on a comparison of the dose data for tracheobronchial and pulmonary regions for the various studies, thresholds were identified for the different effects of concern.

Estimates of deposited dose took into account the duration of inhalation (e.g., 1 minute, 15 s, or a single breath), and attempted to take into account whether the subjects used normal tidal breathing or deeper inhalations (e.g., for single-breath studies). Sensitivity analyses indicated that this uncertainty affected the deposited dose

by less than 20%. However, no adjustment could be made for interruptions of the breathing cycle by capsaicin-induced coughing. Few studies addressed the impact of coughing on pulmonary dose, although, for example, the single-breath studies of Ind et al. (2001a, b, undated), noted that coughing at higher concentrations sometimes kept the subjects from taking a full breath. A similar effect might be expected to apply to all studies at the higher capsaicin concentrations, but insufficient information was available to quantitatively account for the effect of coughing. Coughing would mean that the pulmonary (and perhaps also tracheobronchial) dose would be over-estimated, and thus that the true threshold may be somewhat lower. The uncertainty regarding the aerosol droplet size distribution had a larger impact on dose than the uncertainty regarding depth of inhalation. The default distribution resulted in estimated doses to the tracheobronchial and pulmonary regions almost three times those estimated for narrower distributions. Thus, two of the major uncertainties both result in over-estimates of the dose.

4.2.2 Respiratory Irritation

Cough that results in temporary breathing difficulty is an intended effect for small aerosol droplet sizes, and so the threshold of interest is the lowest dose affecting all of the population. As summarized in Table 3, four studies provided useful data. In the most carefully documented study, and the only one showing cumulative frequency of responders, Doherty et al. (2000) evaluated cough following a single slow inhalation. They found that the median cough threshold (defined as five coughs) was 31 μM in the COPD subjects, 62 μM in the asthmatics, and >500 μM in the normal subjects, with approximately 45% of normal subjects reaching their threshold at the highest tested concentration of 500 μM; these concentrations correspond to estimated TB doses of 0.029, 0.058, and 0.47 μg, respectively. In a study that was generally well-documented but did not provide information on aerosol droplet size variability, Midgren et al. (1992) reported that the highest cough threshold (defined as 2 or more coughs) for a 1-minute inhalation period was 10 μM. This concentration was estimated as corresponding to a TB dose of 0.33 μg, a value in general agreement with the results of Doherty et al. (2000), considering the uncertainties in estimates of deposited dose. Collier and Fuller (1984) reported that the lowest concentration producing cough in all subjects was 4 μM. No information was provided on the nebulizer flow rate or exposure duration, but a relatively tight aerosol droplet size distribution was reported, leading to lower estimates of TB dose than other studies. In addition, unlike other studies where inhalation was via the mouth, inhalation in this study was via a face mask, so inhalation was primarily via the nose. Assuming an exposure protocol duration and flow rate similar to that of the Midgren et al. (1992) study, the TB dose at the threshold is approximately 0.056 μg. While the difference in study design explains why the deposited dose is lower for a given capsaicin concentration in the aerosol, it is not clear why this study identified a lower threshold than the first two studies. However, this lower apparent threshold may indicate that neither concentrations in the aerosol nor deposited dose are fully descriptive dose metrics, and the response depends on both variables. In the final useful study, Blanc et al. (1991) evaluated the cough threshold in capsicum workers and unexposed controls following a single deep breath of capsaicin, and reported that the

lowest concentration at which cough was elicited in all subjects was 6 μM. No information was provided on the aerosol droplet size distribution. Assuming a default size distribution, the TB dose was approximately 0.005 μg.

Thus, there is considerable variability in the estimate of the TB dose causing coughing in all subjects. The data of Doherty et al. (2000) on the median response in normal subjects are used as the basis for the quantitative assessment, since this is the best quality study and the only one providing data on the frequency of responders. The TB dose at the high concentration of 0.47 μg is rounded to 0.5 μg, in light of the numerous uncertainties. It should be noted, however, that some studies indicate a much lower dose is required to elicit cough from all subjects. Conversely, slightly less than half of the normal subjects in the Doherty et al. (2000) study responded at the high concentration. Based on the data in that study, one can estimate that all of the normal subjects would respond at a concentration approximately twice the highest concentration tested. No extrapolation factor is used, since human data are used, and the desire is to identify a dose that will incapacitate all or most of the population. Therefore, the threshold for cough in most of the population (as a surrogate for respiratory incapacitation) is estimated as 0.5 μg to the tracheobronchial region. Note that lower doses could still be effective on a significant percentage of the population, and a dose perhaps twice as high may be required for effectiveness in all normal subjects.

While inhalation of ethanol vapor or small droplets of ethanol can cause respiratory irritation, the ethanol exposure from the PAVA device would be to large aerosol droplets that are too large to be inhaled. Therefore, no dose-response assessment was conducted for respiratory effects of ethanol in the context of the PAVA device.

4.2.3 Bronchoconstriction

Bronchoconstriction is an undesired effect. The lowest threshold for a biologically meaningful effect was identified by Hathaway et al. (1993). An inhaled amount of 0.15 μg to the respiratory tract caused no effect, while a dose of 1.5 μg caused an effect in one asthmatic. The corresponding doses to the tracheobronchial region are 0.033 and 0.33 μg.

As shown in Table 3, an inhaled dose of 6 μg PAVA did not cause a significant decrease in FEV_1 in asthmatics (Ind et al., 2001b); while an inhaled dose of 1.5 μg capsaicin caused a clinically significant decrease in one asthmatic subject (Hathaway et al., 1993). The estimated corresponding tracheobronchial doses were 0.85 μg and 0.33 μg. It is not clear if this difference reflects differences in the subjects studied, or differences between the two compounds. However, Hathaway et al. (1993) found considerable variability among the 17 asthmatics tested, with 15 showing decreases in FEV_1 that did not reach clinical significance, while the two asthmatics with clinically significant changes had thresholds that differed by a factor of 10. Because Ind et al. (2001b) tested only 10 asthmatics, there may not have been a sufficient sample size to capture more sensitive individuals. In particular, Ind et al. (2001b) noted that the absence of effect in their study might not apply to people with severe asthma or

pulmonary disease. Therefore, the threshold from Hathaway et al. (1993) is also applied to PAVA, as a prudent measure.

Identification of the actual threshold requires some broader consideration of the data. The highest tracheobronchial dose with no effect in the Hathaway et al. (1993) study was 0.03 μg, and one sensitive individual responded at 0.33 μg; the actual threshold for response is likely to be between these two doses. Cho et al. (2002) did not observe any bronchoconstriction in asthmatics in a single-breath study at estimated tracheobronchial doses up to 0.37 μg. One capsicum worker was reported as exhibiting bronchoconstriction in a single-breath study at an estimated tracheobronchial dose of 0.0021 μg (Blanc et al., 1991), but this study also reported cough thresholds much lower than those reported by other studies. Thus, many asthmatics and most individuals with normal pulmonary function would not develop bronchoconstriction even at tracheobronchial doses several orders of magnitude above the estimated threshold of 0.03 μg. Conversely, some extremely sensitive individuals may respond at doses below the estimated threshold. Based on these considerations, the threshold is estimated as the highest no effect level in Hathaway et al. (1993), or 0.03 μg. The threshold for normal individuals is >33 μg, based on the absence bronchoconstriction in normals in the Hathaway et al. (1993) study, and the general absence of reports of bronchoconstriction up to doses at least this high. The responding individual in the Blanc et al. (1991) study had never been treated for asthma, but undiagnosed asthma cannot be ruled out.

No extrapolation factor was used, because this threshold was based on a sensitive population, and on a sensitive individual within that population (the most sensitive asthmatic in the study). Therefore, the threshold for bronchoconstriction in normal individuals from capsaicin or PAVA is 33 μg to the tracheobronchial region. The corresponding threshold for bronchoconstriction in sensitive asthmatics is 0.03 μg to the tracheobronchial region. Note that this is latter dose is lower than the dose estimated as a threshold irritation, expressed as the concentration that causes most people to cough Part of this apparent inconsistency is because the bronchoconstriction threshold is intended to cover sensitive populations, while the cough threshold identifies a dose intended to incapacitate a large percentage of the population. In addition, a somewhat lower dose might reduce incapacitation only slightly, while reducing the risk of bronchoconstriction. The comparative dose-response for respiratory irritation and moderate to severe bronchoconstriction is likely to be an important uncertainty in the evaluation of a non-lethal index.

4.2.4 Pulmonary Effects

The threshold for pulmonary effects is based on the results of the study by Reilly et al. (2003a) and Crouch et al. (2003). As described in Appendix C, the deposited dose was calculated from the authors' estimate of 10% deep lung deposition with the deposition fraction calculated for a 125 g rat. Although the estimated pulmonary dose in the Reilly et al. (2002) study is higher than that in the single-exposure study of Debarre et al. (1999), the former study was chosen as the basis for the threshold, because the observed effects in the Debarre et al. (1999) study were of borderline significance. The lethality data of Busker et al. (2001) were not used, because the guinea pig is

hypersensitive to the bronchoconstrictive effects of capsaicinoids. Based on these considerations, a deposited dose to the pulmonary region of 80 μg is the no effect level for SE 2 pulmonary effects in rats. Inflammation was observed at this dose, but no necrosis, hemorrhage, or alveolar emphysema.

Similarly, the threshold for capsaicin identified by Reilly et al. (2003a) and Crouch et al. (2003) is applied to PAVA, because lower doses of capsaicin were tested, and the data indicate that the two compounds had similar potency.

An uncertainty factor of 3 was used to extrapolate from this animal no-SE 2 effect level to the threshold in people. Only toxicodynamic differences need to be considered in the interspecies extrapolation, because the effect level is based on deposited dose. An additional factor of 3 was used to address human variability, focusing on the dynamic aspect, since the dose to the target tissue is the point of extrapolation. The resulting overall uncertainty factor of 10 also takes into account the rarity of reports of effects on lung function after OC exposure, although such consideration is limited by the lack of information on aerosol droplet size in the specific studies. Overall this results in a threshold of 8 μg to the pulmonary region. Note that this value is generally consistent with the absence of pulmonary effects (aside from cough) in the human clinical studies, for which this assessment estimated pulmonary doses up to 3 μg in several studies. In one study, an estimated pulmonary dose of 27 μg was not associated with any reported pulmonary effects beyond cough (Hathaway, 1993).

4.3 Pressure Injury to the Eye

The force of the liquid stream from the OC or PAVA spray has the potential to cause eye injury. Such injury has been reported in a few cases in the field in most studies, where the stream was used at very close range. Based on data from water jets directed at cadaver pig eyes, one can identify a threshold of 20 psi for SE 1 effects, and a threshold of 38 psi for SE 3 effects. Because dose-response data are available (Figure 2), these thresholds actually represent slightly sub-threshold doses. Because the effect is a direct physical one, minimal interspecies differences in sensitivity and minimal inter-individual variability are expected. Therefore, since the “true” threshold is somewhat above these doses, these doses are used directly as estimates of SE 1 and SE 3 effects. Note that these thresholds are expressed as the impulse pressure; lower thresholds would be identified based on steady state pressure.

Ethanol does not affect the dose-response for pressure vs. effects on the eye. The presence of ethanol in the spray does modify the actual pressure from the PAVA spray. This effect was taken into account in the calculations described in Section 5, with the results presented in Section 5.6.2.

4.4 Aspiration

A potential for lung damage resulting from liquid aspiration exists if the target is inhaling with an open mouth at the same time that the stream of OC or PAVA hits the mouth. An effect level of 1-3 mL/kg has been reported for severe, potentially life-threatening effects (Schmidt & Madea, 1995; Fiore & Heidemann, 2004), with no information available on a threshold for less severe effects. A factor of 10 is used to

extrapolate from a severe effect to a dose where that severe effect does not occur. Because the data are for humans, and the starting point is a range, no additional factor for human variability is needed. However, there is considerable uncertainty regarding the factor needed to extrapolate from the effect level to a threshold. Based on these considerations, a reasonable estimate of a threshold for lung damage from liquid aspiration is 0.1 mL/kg, corresponding to 7 mL for a 70-kg adult. Based on a 45 kg body weight for a 12-year-old child (U.S. EPA, 2000), the threshold for a child is 4.5 mL. Ethanol does not affect the dose-response for the effects of aspiration.

4.5 FLAMMABILITY

The flammability potential was calculated based on a model of the saturated air concentration of the solvent from the solvent mixture in the specific preparation of OC or PAVA and the lower explosive limit for the flammable solvent in the mixture used. The lower explosive limit was used for this calculation since it is a measure of the concentration in air that will support combustion. The lower explosive limits for solvents are presented in the Exposure Assessment (Section 5).

4.6 SUMMARY OF DOSE RESPONSE ASSESSMENT

Table 11 summarizes the thresholds for the endpoints evaluated quantitatively in the HERC. The same thresholds were used for PAVA and OC, because insufficient data were available to indicate a clear difference in potency or toxicity.

Table 11. Endpoints Evaluated in the HERC, with Approach Used and Thresholds

Effect	Severity & Effectiveness Level	Threshold	Comments
Eye irritation and blepharospasm	1	50 μg/L (blepharospasm) 0.5 μg/L (eye irritation to bystander)	Intended effect for devices delivering large aerosol droplet sizes
Respiratory irritation	1	0.5 μg to the tracheobronchial region of the lung	Intended effect for devices delivering small aerosol droplet sizes
Bronchospasm in normal individuals	1-3	>33 μg to the tracheobronchial region of the lung	Included in quantitative assessment based on thresholds in human clinical studies
Bronchospasm in sensitive asthmatics	1-3	0.03 μg to the tracheobronchial region of the lung	Included in quantitative assessment based on thresholds in human clinical studies
Pulmonary hemorrhage or alveolar emphysema	2-3	8 μg to the pulmonary region of the lung	Included in quantitative assessment based on thresholds in animal study
Pressure injury from droplets in liquid stream	1-3	20 psi - SE 1 38 psi - SE 3	Included in quantitative assessment based on droplet pressure threshold data from studies with pig eyes
Aspiration	1-3	7 mL for a 70-kg adult 4.5 mL for a 45-kg child	Included in quantitative assessment based on human fluid aspiration thresholds
Flammability	1-3	Solvent-dependent	Included in quantitative assessment based on lower explosive limit

5 EXPOSURE ASSESSMENT

5.1 OVERVIEW

The third phase of the risk characterization is the exposure assessment. The goal of the exposure assessment is to define the interaction between the devices[20] and the user, the target individual, and bystanders. The exposure assessment follows the hazard assessment and dose response sections since the exposure assessment must specify the information necessary to characterize the intended and unintended effects defined in the hazard assessment section using the dose response information.

The exposure assessment begins with the specification of the NLWs that are addressed in the assessment. Once the devices are defined, then the uses of the devices are specified. The use of a weapon is defined in terms of one or more concepts of employment (COE). The COE defines the elements of a use of a non-lethal weapon:

- The user;
- The conditions under which the NLW is used;
- The target(s); and
- The tactical goals for the use.

Based on the COE, factors are identified that determine the interaction of the target and the device, which allow for both the assessment of the device's effectiveness and the probability of unintended effects. Exposures could occur both during the use of the device and under certain conditions at times subsequent to the use. Post-use exposures occur when very small aerosols persist in the air, when particles that settle on surfaces are re-entrained in air, or when individuals come in contact with surfaces contaminated with capsaicinoids.

The physiological and toxicological effects associated with exposures to capsaicinoids from the use of sprays are evaluated by modeling the amount of the spray that reaches different key targets on an individual. These targets are the eye, skin, mouth, and breathing zone. The effective dose or concentration for each of the components of the spray can be derived from the amount of spray reaching the targets.

As discussed above, OC sprays can pose risks to the target other than those from physiological and toxicological effects of capsaicinoids. First, the blunt trauma to the eye from the droplets of the spray may cause injuries from devices that produce high velocity sprays or to individuals impacted at short distances. Second, OC devices that produce streams could result in the aspiration of fluid into the lung. Finally, there is a risk of burns if the solvent in the spray ignites.

The goal of the assessment is to identify the characteristics in the OC devices that have the most influence on the device's effectiveness and risk of unintended effects and then model the variation in the characteristics and the variation in the resultant effects. The exposure assessment will be performed using a number of techniques. Two simulation models were created to investigate the effectiveness of the devices, including the risk of unintended eye and lung effects. A simple physical/chemical model

[20] In this section, the term devices is used generically to address non-lethal devices. The devices evaluated in this report are discussed in the context of the exposure results.

was used to determine the risk for flammability. These models are discussed in detail below and in Appendices F, G, and H.

Post-use exposures to capsaicinoids were not investigated in this assessment. These exposures while sufficient to cause concerns about the decontamination of rooms and individuals, are anticipated to result in doses that are less than those that occur during the use of the devices and therefore are of less concern. Exposures to capsaicinoids in diet are also assessed in this chapter. The assessment is performed to provide a context for intakes of the substances from the devices.

5.2 DESCRIPTION OF THE OC DEVICES

OC devices are a large and diverse set of existing commercial products delivering complex and variable mixtures of capsaicinoids, solvents, propellants, and inert solids. As noted in Section 2.1, there are more than 359 OC devices commercially available (Conrad, 2004). The devices are highly variable and differ in the nature of the aerosol produced, the mixture sprayed, and the concept of employment. This assessment will be limited to the devices that dispense a liquid and are designed to control individuals either in a crowd or on a one-to-one basis. These devices fall into three categories: streams, cone sprays, and foggers. These three categories differ in the size of the droplets produced, the angle of the spray, the presence or absence of a carrier gas, and the velocity of the droplets emitted.

The stream devices emit only a liquid and no carrier gas. The droplets are very large (>500 μm), and the droplets behave as if they were a solid stream. Stream devices have the greatest range of the three categories and are the most resistant to the effects of wind. However, they require the most careful aiming since they must reach the eyes to be effective. The other extreme is the fogger. This type of spray produces much smaller droplets in the 0.5-50 μm size range (UoG, 2004) and often emits the aerosols with a jet of air or propellant to help carry the droplets to the target. (Because of their small size, the droplets do not move well in air.) Foggers do not require careful aiming. The goal of the fogger is to envelop an individual with a cloud of aerosol. When used indoors, a fogger is not necessarily aimed at the target individual, but is used to fill a space or a room with an OC containing aerosol. The cone spray has characteristics that fall between those of the stream and foggers. The cone spray has a farther reach than a fogger and can wet a wide area. As a result, the cone spray does not require careful aiming. The droplet size is intermediate to the other two categories but is typically closer to the stream than the fogger. These three categories are not sharply defined. OC devices that are commercially available form a spectrum from high velocity streams to area foggers.

Capsaicinoids have limited solubility in water. As a result, mixtures in the OC devices are typically a combination of water and water-soluble solvents that enhances the solubility of the capsaicinoids. These solvents are often flammable and many OC devices also contain flammable propellants (e.g., butane and propane). The presence of these flammable component results in a risk of burning if the materials ignite.

OC devices are delivered from pressurized containers. The pressure in the container is determined by the amount and type of propellant and is one of the design criteria for a device. However, the pressure is influenced by the temperature of the can.

A can that is exposed to elevated temperatures (left in a hot car or exposed to direct sunlight) will have higher pressures and the velocity of the droplets will increase.

5.3 CONCEPT OF EMPLOYMENT

As discussed above, the COE for the devices addressed in this HERC is to control a single individual or a crowd. In the case of the cone and stream devices, the devices are assumed to be held at chest high and aimed at the face of a single target individual. The intended target organ is the eye. For the stream, the goal is to have the stream strike the target individual's eyes or to strike the forehead and run down into the eyes. For the cone, the goal is to have the spray wet the face, including the eyes.

The fogger is used in a different fashion than the cone spray or stream. The target of the fogger is the breathing zone of the individual. For the fogger the exact direction of the spray is less important than for the stream or the cone spray. The goal of this use is to envelop the target individual or individuals with a cloud of droplets. In law enforcement applications, foggers are used to clear a space or to disperse a crowd, rather than incapacitating a single individual. Correction agents also use foggers to incapacitate recalcitrant or violent individuals in enclosed spaces. In this use, the nozzle of a fogger is inserted through a small section of a cell door (i.e., the meal slot). The fogger is not aimed at the individual but is used to flood the cell with an aerosol cloud. The individual inhales the aerosol until he or she signals a willingness to cooperate, or until correction personnel determine that the individual can be safely removed.

Individuals can take a number of steps to avoid or minimize the effects of the devices. Prevention of the OC mixtures reaching the eye can be achieved by blocking the spray with the hands or arms, turning the head, or by retreating. These actions in themselves are desirable from the perspective of the user since they block the vision of the target, distract the target, and discourage additional hostile actions. Prevention of inhaling the droplets formed by a fogger can be achieved to some degree by covering the mouth with a cloth or mask. However, such practices require some degree of planning and serve to identify the belligerents in crowds of bystanders. Since OC is not a vapor at normal temperatures it is readily removed by any breathing protection system (i.e., respirator) that filters out small particles.

5.4 CONDITIONS OF USE

All three types of devices can be used both indoors and outdoors. Outdoor use will be affected by the weather. Precipitation and wind can affect the delivery of the spray. As discussed above, the fogger and cone spray are most affected by wind and the stream is the least affected. Since the target organs for OC devices are the breathing zone and the eyes/forehead, the amount of clothing is not a factor in the use of the device. The proposed approach for modeling the devices makes the assumption that wind and precipitation will not be a factor when the device is used and assumes that the fogger is used indoors. These assumptions would lead to exposure predictions that overestimate effectiveness and the risk of adverse effects, since wind and precipitation will tend to reduce the exposure to OC.

5.5 BASELINE SCENARIO FOR OC DEVICES

This wide range of devices containing capsaicinoids poses a significant problem to the design of the exposure assessment. The wide range in characteristics makes it difficult to select a single representative device that could provide a basis for an exposure assessment. The large number of devices makes the assessment of all relevant devices difficult. Finally, the lack of adequate data on any of the many OC devices available makes it impossible to fully assess exposure and risk for a specific device. Given these difficulties, the approach used in this assessment is to perform an exposure assessment for three hypothetical devices that represent each of the three general types of devices, the stream, the cone spray, and the fogger.

In order to assess the exposure for these devices, simulation models were developed for each device. Two models were developed. The first model is an OC module developed for the software program HERCM (Human Effects and Effectiveness Risk Characterization Model). HERCM is a stand-alone software program developed for DoD to evaluate non-lethal weapons. The OC module of HERCM was used to evaluate the Stream and Cone Spray devices. The HERCM model is based on a cone spray or stream being used to control one individual. A second model was developed for modeling the fogger using an Excel™ spreadsheet and a Monte Carlo simulation program, @Risk™. This model is based on the use of foggers in correction facilities to control individuals. This scenario was selected since it presents the potential for higher exposures than other uses.

The use of the foggers has a reasonably high likelihood of resulting in exposure to both the intended individual (the target) and unintended individuals (the user and bystanders), if these individuals are in the same space as the target. However, these doses are not likely to exceed the doses received by the target individual and the target individual exposures are assumed to constitute reasonable upper bound of the exposures for the user and bystanders. Therefore, this assessment has focused on the doses received by the target individuals.

The three illustrative devices are based to the greatest extent possible on three commercially available devices selected for this report, a Brand X Stream, Brand Y Cone, and Brand Z Fogger. These devices were selected as the basis for the three illustrative devices because they have relatively large amounts of information available; however, as Tables 12 and 13 indicate, none of the three devices have sufficient information to perform a detailed exposure assessment. In all cases, the exposure assessment required additional assumptions on factors such as the distribution of droplet sizes and pattern of the spray with distance, and nozzle velocity of the droplets. These assumptions are based on the professional judgment of the authors and reflect the input of users, subject matter experts (SMEs), and manufacturers. As a result, the findings of this analysis cannot be used to make device-specific findings for Brand X Stream, Brand Y Cone, and Brand Z Fogger, or any other specific commercial device. However, the assessment provides insight to risks and effectiveness of the general types of devices. In addition, the approach provides insights to characteristics of the OC devices that are associated with elevated risks.

Table 12. Source of Data Used in Modeling Illustrative Stream and Cone Spray Devices.

Inputs	Basis for Stream Device	Basis for Cone Spray Device
Concentration of capsaicinoids	Manufacturer Data	Manufacturer Data
Concentration of solvent	Manufacturer Data	Manufacturer Data
Density of spray	Manufacturer Data	Manufacturer Data
Volume sprayed per second	Manufacturer Data	Manufacturer Data
Velocity of spray at nozzle	Professional Judgment	Professional Judgment
Spray duration	Manufacturer Data	Manufacturer Data
Angle of spray (dispersion)	Professional Judgment	Professional Judgment
Fraction of spray that hits the face	Professional Judgment	Professional Judgment
Fraction of spray that hits the eyes	Professional Judgment	Professional Judgment
Fraction of spray that hits the mouth	Professional Judgment	Professional Judgment
Distribution of droplet sizes	Professional Judgment	Professional Judgment

Table 13. Source of Data Used in Modeling Illustrative Fogger Device.

Source of Data Used in Modeling Illustrative Fogger Device	
Input	**Basis**
Concentration of capsaicinoids	Manufacturer Data
Concentration of solvent	Professional Judgment
Concentration of inert solids	Manufacturer Data
Specific Chemical used as a solvent	Professional Judgment
Vapor Pressure of Solvent	Professional Judgment
Molecular Weight of Solvent	Professional Judgment
Activity coefficient of solvent in water	Professional Judgment
Spray duration	Manufacturer Data
Volume sprayed per second	Manufacturer Data
Distribution of droplet sizes	Professional Judgment

Brand X is a stream spray and Brand Y is a cone spray. The characteristics of the two devices are as follows:

Ethanol 50%, Vol
Water 50%, Vol
PAVA 0.3%, Wt. vol
Density of spray 920 kg/m^3
Spray rate 8.5 mL/s (stream), 6.8 mL/s (cone)
Spray Duration 0.5 s

Data were provided on the distribution of droplet sizes for both devices in a study by Marshall and Knight (2000). This study can be used to set a reasonably lower limit to the droplets produced by both devices (100 μm). Unfortunately, this study cannot be used to define the distribution of droplet sizes because the study did not define the distribution of sizes above 500 μm. Therefore, the distribution of droplet sizes for the

two devices is developed based on a consideration of the size of the droplets required to reach the 5 meter effective range and professional judgment. The stream is assigned lognormal distribution with an arithmetic mean of 2000 and standard deviation of 200 (geometric mean of 1990 μm and a geometric standard deviation of 1.4 μm). The cone spray is assigned a distribution of droplet sizes that is lognormally distributed with an arithmetic mean of 1000 and standard deviation of 500 (geometric mean of 880 μm and a geometric standard deviation of 4.3 μm). The spread angle of the stream and the cone sprays are estimated to be 0.23° and 20°, respectively. The spread angle is defined as the angle that encompasses the spray measured from the center of the spray to the outer edge. A larger spray angle indicates a wider spray and a more rapid attenuation of the spray with distance. Appendix G provides additional information on the spray angle.

In order to model the devices, an estimate of the velocity of the droplets at the nozzle is required. A value of 17 m/sec was used for both the stream and cone spray. The value is based on professional judgment and reflects a simple visual examination of the height that the stream from a Brand X Stream reaches and the relationship between the peak height reached by an object and the object's initial velocity. The device used was at room temperature. Since the pressure in the Brand Y Cone is the same as the Brand X Stream the same velocity is used for that device.

The fogger modeled in this analysis is a generic mixture based on the Brand Z fogger. This device was selected since it had information on the composition of the spray and the amount used. The characteristics of the device as reported by Conrad (2004) are as follows:

Solvents: alcohol base (specific alcohol not identified)
%OC: 10% Wt. vol
Total Capsaicinoids: 0.33 %
Spray rate[21]: 29 mL/sec
Spray duration: 1 s

Because the exact composition of the solvent mixture in the Brand Z fogger is not known, an assumption is made that the solvent is assumed to be a mixture of 50% ethanol and 50% water. Data on the droplet sizes produced by the fogger are not available; however, foggers are generally intended to produce aerosols from 0.5-50 μm (UoG, 2004). In the illustrative fogger the distribution of droplet size is assumed to follow a lognormal distribution with an arithmetic mean of 20 and standard deviation of 20 (geometric mean of 14 μm and a geometric standard deviation of 14 μm).

5.6 Effects Considered in the Exposure Assessment

In Section 3 of this report, seven effects of OC devices were identified as having potential concern and adequate data to develop dose or concentration-response

[21] Based on a reported total weight of 519 g per can and the description that each can provides 18 one second sprays.

information in Section 4. Some of these effects will be more important than others for individual types of OC devices.

OC devices differ in their target organs, based on the size of the droplets that are formed. As shown in Figure 5 below, devices that generate droplets with diameters greater than 100 μm primarily target the eye. These larger droplets will impact the eyes and produce ocular effects. In contrast, droplets below 100 μm are not expected to land efficiently on the surface of the eye. These smaller droplets lack the kinetic energy to act via impaction mechanisms; rather they tend to stay in the air stream and flow around individuals' heads. For this reason, ocular exposure to the smaller droplets is not considered in this exposure assessment, although the action of turbulence and local forces (e.g., electrostatic mechanisms) could result in some eye exposure. The opposite relationship between droplet size and potential exposure holds true for the respiratory tract. As Figures 4 indicates, droplets in the range of 100 μm are difficult to inhale and if inhaled impact in the nose and mouth. Droplets must be <40 μm to be inspired, with the amount reaching the tracheobronchial and pulmonary portions of the respiratory tract dependent on their size. Particles in this size range cause the intended effect (respiratory irritation) and unintended effects (bronchospasm and pulmonary effects). As a result, devices that produce smaller droplets primarily target the breathing zone and the respiratory tract.

These two discrete size ranges allow designers of OC devices to choose which of the target organs they wish the devices to affect. Thus, the same mixture of capsaicinoids will target the eye in one device and target the lung in another.

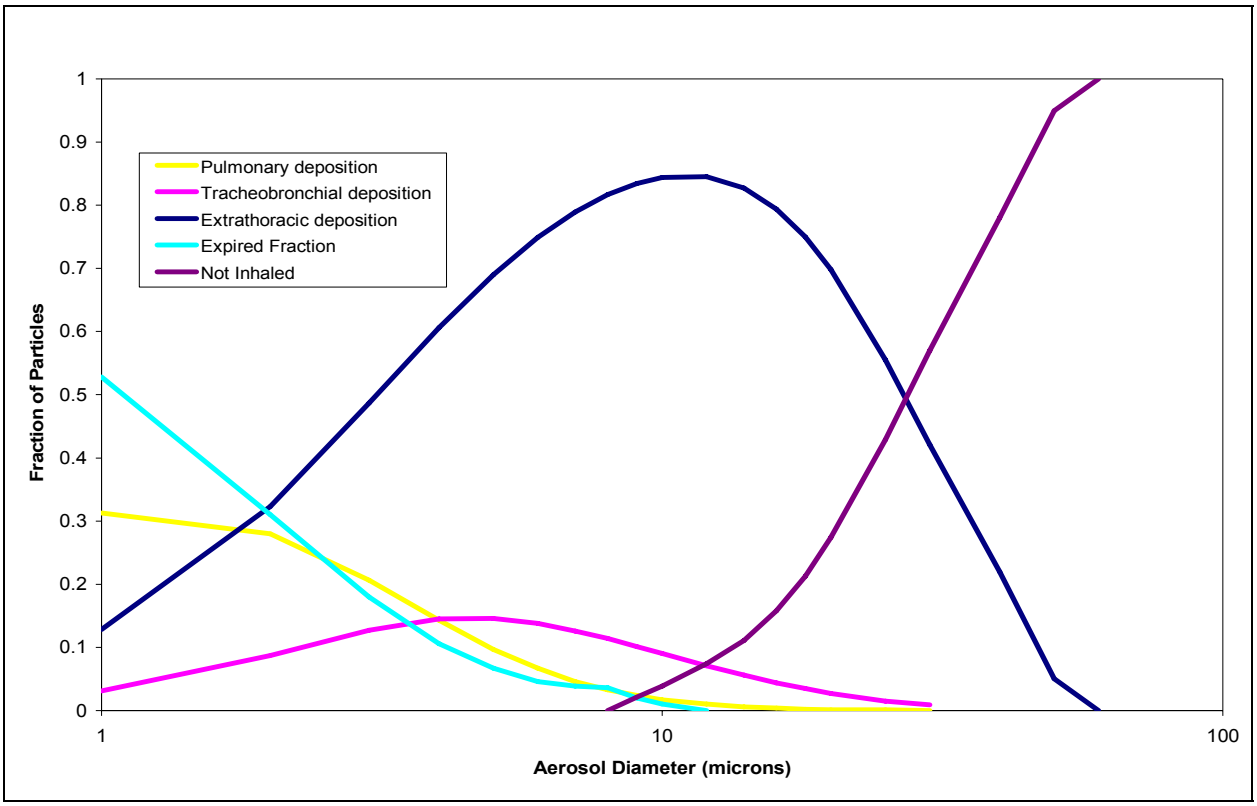

Figure 4. Particle Size and Inhalation Exposure (Source USEPA, 1994).

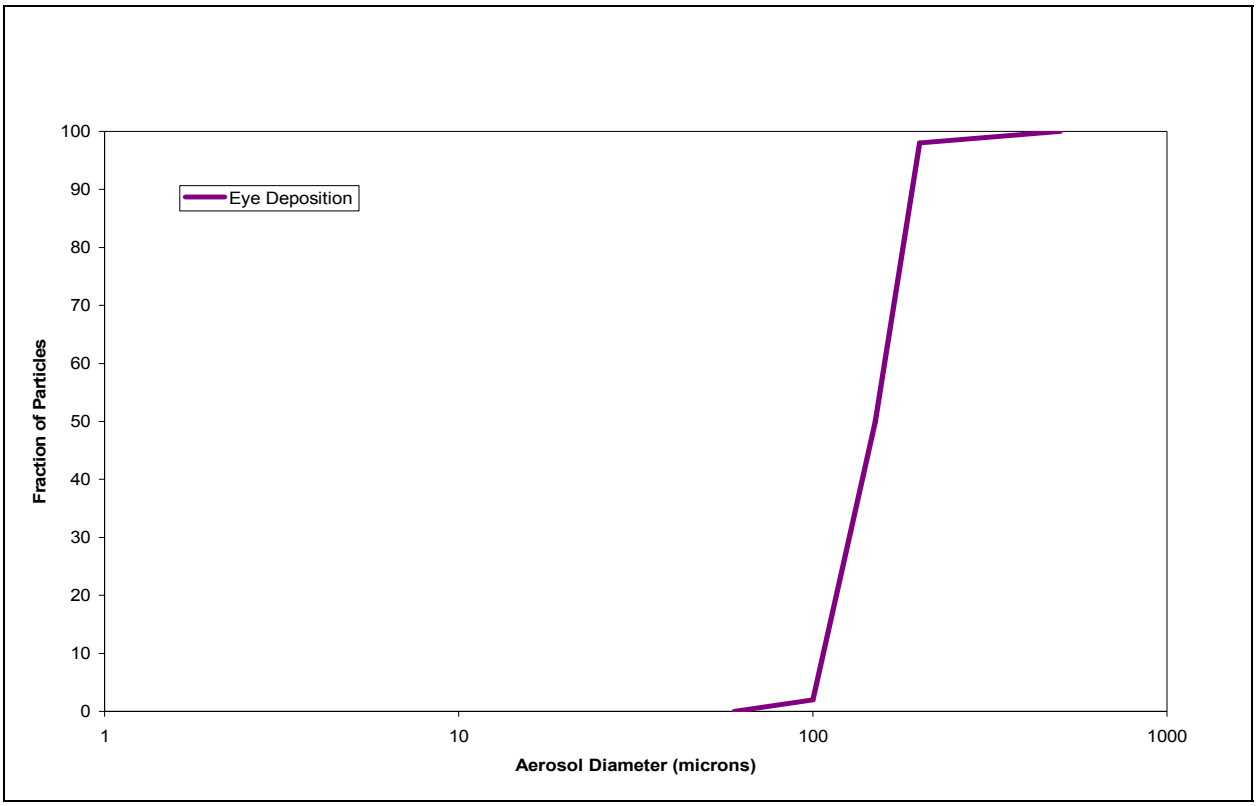

Figure 5. Particle Size and Eye Exposure (Hinds, 1999).

Streams also have the potential to cause the aspiration of the mixture used in the device into the lung. These devices can, in theory, deliver a large volume of liquid to the back of the throat that could in turn be drawn into the lung. This would not be expected to occur for the cone spray and fogger since these categories of devices disperse the spray mixtures over a wide area and only a small fraction of the volume sprayed would enter an open mouth.

Streams also have the potential to enter the nose as well as the mouth. Such exposures are likely to trigger strong irritation but as discussed in the effects section of this report are not likely to cause other effects. For this reason, the amount of a stream entering the nose will not be evaluated in the exposure assessment.

OC devices contain propellants and solvents that are flammable. Flammable propellants are not evaluated in this assessment since they are expected to be diluted to concentrations below the lower explosive limit within a few feet of the device. The solvents, however, can reach a target individual, saturate the skin or clothing, and pose a risk of catching fire if a source of ignition is present. Flammability is a concern for the stream or cone spray. Foggers produce a disperse cloud of small droplets that generally do not land on clothing.

Table 14 presents a summary of the effects that are investigated in this exposure assessment.

Table 14. Effects Modeled in the Exposure Assessment.

Effect	Target	Applicable for Stream	Applicable for Cone Spray	Applicable for Fogger
Eye irritation and blepharospasm	Eye	Yes	Yes	No
Pressure injury from liquid stream	Eye	Yes	Yes	No
Respiratory irritation	Respiratory System	No	No*	Yes
Bronchospasm	Respiratory System	No	No*	Yes
Pulmonary hemorrhage or alveolar emphysema	Respiratory System	No	No*	Yes
Aspiration	Mouth/Throat	Yes	No	No
Flammability	Clothing	Yes	Yes	No

*Some cone sprays may include respirable size droplets. If so, they could cause effects in the respiratory system.

5.6.1 Modeling Exposure of the Eye to Capsaicinoids, Inert materials, and Solvents in OC Sprays

OC devices deliver a spray mixture to the eye by either producing droplets that directly impact on the eye or which hit the forehead and run down into the eyes. The capsaicinoids will immediately trigger lacrimation that will dilute and ultimately remove the capsaicinoids. However, the initial dose seen by the cornea is a function of the volume of tear on the eye, the volume of the spray mixture that reaches the eye, and the concentration of the components in the spray mixture. The initial concentration of the capsaicinoids is given by the following equation:

$$Conc_{eye} = Vol_{eye} * Conc_{Caps} / (Vol_{eye} + Vol_{tear})$$

where:

Vol_{eye} is the volume of the spray mixture that reaches the eye.
$Conc_{Caps}$ is the concentration of capsaicinoids in the mixture.
Vol_{tear} is the volume of the tear in the eye.

The volume of tear in an eye is quite small. Shimizu et al. (1993) and Hirase (1994) report a range of volumes of 12.4 ± 6.2 μL per eye in 30 healthy volunteers. This small value for the initial tear volume is approximately the same as the volume of a single large droplet (with a diameter of 3,000 μm). Thus, a relatively small number of the large droplets formed in the cone sprays and streams will easily overwhelm the tear volume in the normal eye.

Capsaicinoid exposure in the eye is inherently self-limiting. The volumes of spray mixture that can be retained are limited by the capacity of the eye to hold extra fluids. Prokai (2004) reported that volumes of fluids beyond 30 μL will not be retained

by the eye and will simply run off. More importantly, the highest concentration that is seen by the eye is the concentration of the undiluted spray mixture.

In this assessment, the ocular exposure of the eye to capsaicinoids is characterized in two ways. First, the total mass of capsaicinoids in the spray that hits the eye is reported. This amount is capped at 30 μL since any additional fluid will run off the eye and not reach the eye. Second, the initial concentration of the capsaicinoids in the eye is reported based on the equation given above.

The duration of contact of capsaicinoids, solvents, and inert solids with the eye is expected to be brief. The high level of pain will cause an individual to close their eyes, turn their head, and cover their eyes with their hands. This will limit the duration that the eyes receive the spray. OC is a powerful lachrymator that will induce copious tearing that will rapidly reduce the concentration of OC, solvents, and inert solids in contact with the eye.

This assessment of ocular exposures does not include a quantitative estimate of the exposures of the solvent or inert solids. As with the capsaicinoids, the upper bounds of the concentrations of these components that reach the eye are the concentrations of the components in the original spray. See Section 2.3 for additional information on solvents.

5.6.2 Modeling Risk of Eye Damage

As discussed in Section 4.3, thresholds for eye damage from the impact of a droplet can be evaluated based on the pressure that the droplet exerts on the portion of the eye that the droplet hits. The pressure on the eye produced by the impact of a single droplet is a complex finding that is determined by the physics of the interaction of a liquid droplet and a solid surface. The approach used in this report is to determine the pressure based on the following equation (J.H. Stuhmiller, personal communication, 2004) that relates the density of the fluid and the velocity of the droplet to the pressure exerted on the eye.

$$\text{Pressure (Pa)} = 1/2\ \rho\ V^2$$

where

ρ is the density of the spray in kg/m^3
V is the velocity of the droplet in m/s

The density of the spray can be approximated based on the composition of the mixture and the densities of the solvent and water. For a 50/50 by weight mixture of ethanol and water, the density will be approximately 900 kg/m^3. For a spray that is largely water, the density could be as high as 1,000 kg/m^3. Sprays composed of only oxygenated solvents may have densities as low as 800 kg/m^3.

Table 15 presents the droplet velocities that correspond to the eye damage benchmarks of 20 psi for SE 1 and 38 psi for SE 3 for OC mixtures of different densities.

Table 15. Droplet Velocities (m/s) Corresponding to Pressure Benchmarks.

Density (kg/m^3)	SE 1 (20 psi)	SE 3 (38 psi)
800	19	26
900	18	24
1000	17	23

5.6.3 Modeling Risk of Respiratory Effects

As discussed above, the illustrative devices for the stream or cone sprays did not consider respiratory effects since the available data suggested that the droplets produced by these devices are too large to be inspired. This section describes the modeling of respiratory effects for the foggers. The same approach could be applied to cone sprays that generate respirable droplets.

Respiratory effects are modeled in terms of the dose of capsaicinoids that reach different portions of the lung. As discussed in detail below, the approach used in this assessment is to model individual droplets and, based upon the size of the droplets, determine if the droplet delivers a dose to one of the three regions of the respiratory tract, extrathoracic, tracheobronchial, or pulmonary.

In order to explore the respiratory tract dose that would occur, a model of droplets in a small room (cell) was used to estimate the doses received by an individual during and after the use of a fogger. Separate doses were determined for the extrathoracic, tracheobronchial, and pulmonary regions of the respiratory tract. The probability of the deposition of droplets of different sizes in the different regions is calculated using the RDDR software developed by the USEPA (1994), (see Table 16). Note that these are cumulative probabilities, not the probability of deposition in the specified region. For example, the probability listed in the tracheobronchial region reflects the total probability of a particle being exhaled with no respiratory tract deposition, depositing in the extrathoracic region, or depositing in the tracheobronchial region. Because the maximum particle size considered by the RDDR software is 30 μm, percentages for larger particle sizes were calculated assuming a linear interpolation between 30 and 50 μm.

Table 16. Cumulative Percentages of Inhaled Droplets that are Exhaled or Deposited in One of the Three Compartments of the Respiratory System.

Cumulative Percentages of Inhaled Droplets				
Size (μm)	**Exhaled**	**Extrathoracic**	**Tracheobronchial**	**Pulmonary**
1	53	66	67	100
2	31	63	72	100
3	18	67	79	100
4	11	71	86	100
5	6.7	76	90	100
6	4.6	80	93	100
7	3.9	83	95	100
8	3.6	85	97	100
9	4.1	88	98	100
10	4.9	89	98	100
11	6.2	91	99	100
12	7.4	92	99	100
13	9.3	93	99	100
14	11	94	99	100
15	13	95	99	100
16	16	95	100	100
17	19	96	100	100
18	21	96	100	100
19	24	97	100	100
20	27	97	100	100
21	31	97	100	100
22	34	98	100	100
23	37	98	100	100
24	40	98	100	100
25	43	98	100	100
26	46	99	100	100
27	49	99	100	100
28	51	99	100	100
29	54	99	100	100
30	57	99	100	100
31	60	99	100	100
32	63	99	100	100
33	65	99	100	100
34	68	99	100	100
35	71	99	100	100
36	74	99.	100	100
37	76	100	100	100
38	79	100	100	100
39	82	100	100	100
40	84	100	100	100
41	86	100	100	100
42	88	100	100	100
43	89	100	100	100
44	91	100	100	100
45	92	100	100	100
46	94	100	100	100
47	95	100	100	100
48	97	100	100	100
49	98	100	100	100
50	100	100	100	100
>50	100	100	100	100

5.6.4 Modeling Aspiration of Liquids

As discussed in Section 3.5.5 of this report, liquids aspirated into the lung can cause serious effects. A number of steps must occur for the aspiration of the OC spray mixture:

- The liquid stream must enter an open mouth;
- The liquid must reach the back of the throat independent of the normal swallowing mechanism; and
- The individual must be in the process of inhaling air into the lungs.

This scenario is plausible for the stream devices where it is reasonable to assume that an individual may have his or her mouth open and be breathing heavily. If the head is held at an angle where the mouth and the back of the throat are lined up exactly parallel to the stream, the stream could enter the mouth and strike the back of the throat. If the person was inhaling, the spray mixture could be aspirated into the lung. The probability of this occurring will depend on a number of factors that are difficult to predict, such as the position of the head relative to the stream and the fraction of the dose that enters the mouth that will reach the throat. No sources of data have been identified for these factors and they cannot be readily predicted from human physiological data or theoretical considerations.

This effect is not a concern for cone sprays or foggers. These devices release a pattern of spray that is very wide relative to the size of an open mouth as a result only a small amount of the amount of the OC mixture sprayed could enter the mouth.

In this assessment, the approach used to evaluate the potential for the aspiration of OC mixture is to determine if it is possible for a device to place a sufficient volume of the mixture into an area the size of the human mouth (a circle with a radius of 2 cm). This is determined by the amount of liquid sprayed in a given use, the fraction that hits the face, and the amount that falls on an area equal to the size of an open mouth. The first factor can be based on the manufactures' description of the device; the second factor will vary from use to use. The final factor is a function of the how fast the stream spreads with distance and the distance to the target individual.

This is not the same as a determination of the amount that could be aspirated. Due to the complexity of the factors determining whether the stream is aspirated once it hits the mouth, no attempt was made to estimate the fraction of the stream that would be actually aspirated. Instead, the result of this modeling is simply the volume that may hit the mouth area and if the mouth is open to enter the mouth.

5.6.5 Modeling Flammability

The potential for flammability of an OC mixture was determined using the conservative approach of determining if the mixture will produce a concentration of solvent in air that exceeds the Lower Explosive Limit of the solvent under conditions of saturation. This determination is then used to specify a maximum concentration of the solvent in water. This criterion was adopted because a solvent mixture on clothing will rapidly evaporate and saturate the air in the voids in clothing (the small spaces between

fibers). The air space adjacent to the saturated clothing that exceeds the Lower Explosive Limits (but is below the Upper Explosive Limit) would then support combustion if an open flame were present at the surface of the clothing or if an arc was passed through the clothing (for example from a conducted energy device). The process is described in detail in Appendix D, Modeling Flammability of OC Sprays.

This finding does not indicate that ignition of the solvent will always occur if an open flame is near an individual sprayed by a device. In fact, mixtures with solvent levels well above this may not ignite in the presence of cigarettes or other small sources of heat.

This process was performed on the solvents reported by Conrad (2004) to be used in OC sprays. These solvents are isopropanol, ethanol, sec-butanol, propylene glycol, diproplyene glycol methyl ether, and d-limonene[22].

5.7 Modeling the Interaction of the OC Cone Spray and Stream and the Individual (the HERCM Model)

The stream and cone spray are used to control individuals in one-on-one confrontations by causing eye effects. As Table 9 indicates, the effects for the cone spray are irritation and blepharospasm resulting from the dose to the eye and pressure injuries to the eye. The effects for the stream are irritation and blepharospasm resulting from dose to the eye, pressure injuries to the eye, and pulmonary effects resulting from aspiration of liquid. The dose to the eye will be described in terms of the mass of capsaicinoids that reaches the eye and the concentration of the capsaicinoids in the fluid in contact with the eye. The pressure to the eye is described in units of pounds per square inch (psi). Data on the two PAVA devices indicates that the neither of the devices produces droplets that are sufficiently small to be inhaled (Marshall & Knight, 2000)[23]. In addition, the droplets striking the face do not appear to generate large amounts of respirable aerosols (Marshall & Knight, 2000). This appears reasonable for these devices, since such small droplets would not travel more than 30 to 60 cm before being stopped by wind resistance, and thus would pose more risk to the user than to the target. The aspiration of liquid is characterized in terms of the volume of liquid that could be “squirted” into the mouth; the probability of such an event is not characterized.

The approach used to model the exposures to capsaicinoids from the use of these devices is a model of the generation and transport of droplets. The HERCM module for OC creates a trajectory for each of 10,000 to 100,000 droplets and determines if the droplets hit the target individual’s face or their eyes. The model takes into account the velocity of the droplets at the nozzle, the direction of each droplet, and the effects of wind resistance (drag) and gravity[24] to determine the velocity of each droplet at the eye. The location of the target’s breathing zone and eyes are defined. The location of each droplet is modeled over time to determine if the droplet hits the eye

[22] d-limonene also has limited water solubility and is likely added with other solvents.

[23] Cone sprays from other manufacturers are described as targeting the lung as well as the eye. This is possible if the cone sprays generate sufficiently small droplets. Such droplets would not travel far unless a carrier gas is emitted with the droplets that would carry the droplets to the target individual. Such devices would be best evaluated using the fogger scenario discussed below.

[24] Droplets at the small end of the size range are also influenced by electrostatic effects. The impacts of such effects were not considered in this model.

or the target individual's breathing zone. The HERCM module for OC is described in detail in Appendix G.

Separate versions of the model are developed for the stream and cone sprays. The reason for the two versions is that the two devices are used in different ways. In the case of the stream, the person is assumed to be moving and only a fraction of the stream hits the individual's face. The model does not attempt to define the actual three-dimensional weaving and bobbing that a suspect may take in response to firing an OC device. Rather, the user enters a simple estimate of the fraction of the spray that is centered on the person's face. When the device is not aimed at the face then exposure from the stream is assumed to be minimal. In contrast to the stream, the cone spray rapidly spreads out after being fired and within a meter is sufficiently wide that it can be assumed to constantly cover the target's face during a use.

5.7.1 Modeling Stream Devices

The stream model is based on the concept that the stream is aimed at the face and in particular the eyes. The duration of the spray is typically a second or less. The target individual may respond by turning his head, moving his body, or blocking the spray with his arms so that only part of the stream reaches the face. To model this process the manufacturer's recommended duration of spray is multiplied by the fraction of time the spray is hitting the target's face. The equation used for this is as follows:

$$Vol_{face} = Vol_s * Fract_{face}$$

where:

Vol_{face} is the volume of the spray mixture that hits the individual's face.
Vol_s is the volume of the spray mixture emitted by the device during the recommended spray duration.
$Fract_{face}$ is the fraction of the time the spray is aimed at the face.

In this analysis, the time of spraying the stream is 0.5 s and the spray rate for the stream is 8.5 mL/s. The $Fract_{face}$ is assumed to vary from use to use and range from 0.4 to 1. This assumption is based on professional opinion and may over- or underestimate the exposures for individual devices.

The fraction of the Vol_{face} that hits the eyes or the mouth will vary from use to use. In this assessment, the volumes are estimated using the following equations.

When: $Area_{mouth} > Area_{spray}$

$$Vol_{mouth} = Vol_{face} * Fract_{mouth}$$

When: $Area_{mouth} < Area_{spray}$

$$Vol_{mouth} = Vol_{face} * Fract_{mouth} * Area_{mouth} / Area_{spray}$$

When: $Area_{eye} > Area_{spray}$

$Vol_{eye} = Vol_{face} * Fract_{eye}$

When: $Area_{eye} < Area_{spray}$

$Vol_{eye} = Vol_{face} * Fract_{eye} * Area_{eye} / Area_{spray}$

where:

Vol_{mouth} is the volume of fluid that could enter the mouth.
$Fract_{mouth}$ is the fraction of the time a portion of the stream strikes the mouth.
$Area_{spray}$ is the cross-sectional area of the stream at a given distance between the user and the target individual.
$Area_{mouth}$ is the area of an open mouth (12 cm^2).
Vol_{eye} is the volume of fluid that strikes the eye
$Fract_{eye}$ is the fraction of the time a portion of the stream strikes the eye.
$Area_{eye}$ is the area of an eye (5.2 cm^2/per eye)

The fraction that could strike the mouth and the eye vary from use to use. The range of these values is assumed to be a uniform distribution from 0.01 to 0.06 for the mouth and 0.05 to 0.25 (for one eye). The basis for this range is professional judgment based on a consideration of the relative area of the face, one eye, an open mouth and the intent of the user to aim for the eyes. This distribution is also intended to account for the impact of spray running into the eyes from the forehead. Because of the uncertainty within the factor, the resulting values may over- or underestimate the exposures for individual devices.

The terms $Area_{mouth} / Area_{spray}$ and $Area_{eye} / Area_{spray}$ are correction factors to account for the fact that at larger distances the area of the eye and mouth are smaller than the cross-sectional area of the stream. Thus, some portion of the spray will miss the eye and mouth even when aimed directly at these anatomical targets.

The area of the spray is derived from the modeling of the trajectories of individual droplets in the sprays. As described in Appendix G, the cross-sectional area of the stream increases with distance. Table 17 presents the cross-sectional areas for the spray at different distances as estimated in Appendix G.

Table 17. Spread of the Stream Device with Distance Based on Droplet Simulation Model.

Distance to Target Individual (m)	Cross-sectional Area of Spray (cm^2)
1	3
2	6
3	39
4	87.5
5	196

The stream devices such as the Brand X Stream are described as a stream of fluid but in fact, the stream separates into large droplets shortly after leaving the nozzle. These droplets are then slowed by the wind resistance. The pressure that the droplets exert on the eye, based on the density of the mixture sprayed, the velocity predicted to occur at the eye and the equation described in Section 5.5.2. The density of the spray mixture used in the assessment is taken from data on the mixture used in the Brand X stream spray (920 kg/m^3).

5.7.2 Modeling Cone Sprays

Modeling cone sprays differs from the stream devices in that some portion of the cone can be assumed to strike the target's face during the entire time the device is operated. However, even at close distances the majority of the spray will miss the face since it is dispersed over a wide area. The spray is assumed to be uniformly distributed across the "cone" formed by the spray. The size of the cone and thus the density of the spray will decrease with the distance between the user and the target individual. With an angle of spread of 20°, the area struck by a cone at one meter will be 3,700 cm^2; a face with an area of 433 cm^2 will take up 12% of the spray. An eye with an area of 5.2 cm^2 will take up 1.4% of the spray.

The droplet model for the cone sprays defines the location of the eyes and determines for each droplet whether the droplet hits the eyes. If the droplet strikes an eye, then the volume of the droplet and its velocity are determined. The results of the model are used to estimate the volume of the droplets that strike the eye. While the number of droplets modeled is large (10,000), these droplets represent less than 1% of the total volume sprayed. Thus, the volume of the droplets striking the eye has to be multiplied by the ratio of the total volume sprayed to the total volume of the droplets simulated.

$$Vol_{eye} = (\Sigma\ Vol_{ie})^* Vol_s / (\Sigma\ Vol_i)$$

where:

Vol_{ie} = is the volume of the i^{th} droplet that strikes the eye.
Vol_i = is the volume of the i^{th} droplet modeled.

5.7.3 Modeling Inhalation Exposures from OC Foggers

As discussed above, the target for the fogger is the respiratory system, not the eye. Foggers produce aerosols that are too small to affect the eye or even to affect the face. Since the devices are not pointed at an individual as a directed jet of fluid, there is little chance of fluids being inspired into the lungs. As a result, the effects that are relevant to the fogger are the doses that are delivered to the tracheobronchial and pulmonary portions of the respiratory system via inhalation.

Modeling exposure to a fogger used indoors requires consideration of a number of processes, including removal mechanisms and changes in the size of the droplets[25]. Once released into the cell, droplets will eventually be removed from the cell air by one of four processes. These are:

- Removal by the ventilation system or leakage around the cell door;
- Settling to the floor;
- Adhesion to the wall, ceiling or other surfaces; or
- Inhalation by the individual.

The last two processes are believed to remove a very small proportion of the droplets, based on the following rationale. Foggers are designed to generate droplets in the size range of 0.5 - 50 μm. Droplets this small do not contact solid objects, but flow around them with air currents. As a result, they may settle out to the floor but they do not come into contact with walls or ceilings. The volume of air inhaled by an individual is a small fraction of the total volume of air in a cell, and the removal by this route has a minimal effect on the fate of an aerosol droplet. The remaining two processes, settling and ventilation, need to be addressed. The rate of settling is determined by the size of the droplet. Because of their small size and the time they remain airborne; droplets in foggers lose their solvent and shrink in size. As the droplets shrink, their settling rate decreases.

The approach used to model this scenario is to model the individual droplets in the room over time. This approach allows the model to determine the joint effects of removal and evaporation. The result of this modeling is a determination of the composition of the aerosol in the room over time. This composition includes the number of droplets in a given volume of air and the distribution of the size of the droplets. This approach allows for the characterization of the density of droplets in the air that the individual inhales at various points in time, the portion of the droplets that are retained in the respiratory tract, and the fraction that are deposited in each region of the respiratory tract. Details on this model are provided in Appendix H.

In this assessment, the model tracks 10,000 droplets over a 20 minute period. The distribution of the droplets is determined at selected times (0.167, 0.333, 0.5, 0.667, 0.833, 1, 2, 3, 5, 10, and 20 min). The model then uses the data in Table 18 to determine whether an inhaled droplet is deposited in the extrathoracic,

[25] Droplets can also coalesce to form larger droplets that would have higher settling rates. Droplets in this size range; however, tend to move with the bulk transport of air. Because of this the number of collisions between droplets of this size is small and the formation of larger droplets is not expected to be a significant factor.

tracheobronchial, or pulmonary region of the respiratory tract. If the droplet is deposited, then the mass of capsaicinoids in the droplet is counted as a dose for that portion of the lung. Finally, the total dose to each portion of the lung is determined using the following process. The volumes of the 10,000 droplets modeled were totaled to determine the total volume of spray simulated in the model. This volume (typically <0.00001 mL) is much smaller than the actual amount of mixture sprayed in a use. The dose estimates were then increased by a factor equal to the volume sprayed divided by total volume in the 10,000 modeled droplets. For example, in the case of the pulmonary dose the equation used is as follows:

$$\text{Total Mass}_{Pul} = \text{Mass}_{Pul} * \text{Vol}_s / (\Sigma\ \text{Vol}_i)$$

where:

Total Mass_{Pul} is the actual dose to the pulmonary portion of the lung.

Total Mass_{Pul} is the total dose contained in the droplets that deposit in the pulmonary portion of the lung.

Vol_s = is the volume of the mixture sprayed in the cell.

Vol_i = is the volume of the i^{th} droplet modeled.

The simulation model of exposure to OC from a fogger was applied to the illustrative fogger. As discussed above, this fogger was based on a mixture used in the Brand Z Fogger and the rate of spray released from that fogger. A one-second spray is assumed that introduces 29 mL of liquid into a cell. The liquid is assumed to be in the form of a fog with a lognormal droplet size distribution with a geometric mean diameter of 14 μm and geometric standard deviation of 1.4 μm. This assumption is based on professional judgment and may or may not be representative of the Brand Z Fogger or any other device.

The room where the fogger is used is assumed to be a prison cell with a ceiling height of 2.4 m and a total room volume of 10 m^3. The cell is assumed to have a low air exchange rate (0.5 exchanges per hour), because vents would have been closed to avoid the circulation of the OC aerosol to other cells. The individual is assumed to be an adult male[26] with an elevated breathing rate (due to stress) of 2.0 m^3/hr. Since a single breathing rate is assumed and since a single concentration is solved for at each point in time, there is only a single value derived from this model. Actual doses will vary with the breathing rate of the individual. The range in peak breathing rates in adults is small (US EPA, 1997) therefore the range in dose is also expected to be small.

5.8 RESULTS

5.8.1 Results for Stream and Cone Sprays

The results of two models are given in Tables 18 through 20 As discussed in Appendix G this analysis is based on the assumption that wind is not an issue during use. The range of 1 to 5 m was selected since the maximum distance of the stream

[26] Female breathing rates would be slightly smaller resulting in lower doses.

and cone sprays in the simulation model was found to be between 5 and 6 m and many manufacturers' specify that devices should not be used at distance of less than 1 m.

Table 18 presents the predicted doses to the eye of PAVA and the volume of fluid that could potentially be aspirated into the lung. The range of high and low values comes from the estimate of the fraction of the time the spray hits the target of interest (eye or mouth). The values presented are the 5th and 95th percentile of the distribution of Vol_{eye} and Vol_{mouth}.

Table 18. Predicted Exposures to the Eye and Mouth for Stream Device at Five Distances.

	Distance (m)				
	1	**2**	**3**	**4**	**5**
Dose to Eye (mg)					
Low	9.0E-02	9.0E-02	4.9E-02	2.2E-02	9.7E-03
High	9.0E-02	9.0E-02	9.0E-02	9.0E-02	9.0E-02
Eye conc. (µg/L)					
Low	2000	2000	1700	1100	600
High	2000	2000	2000	2000	2000
Estimate of Aspirated Liquid (ml)					
Low	0.2	0.2	0.07	0.03	0.01
High	0.3	0.3	0.1	0.04	0.02

As Table 18 shows, the upper bound of the range of eye doses and the resulting concentrations of PAVA in the eye are limited by the capacity of the eye to retain liquids. At distances of less than 2 m, the lower bound of dose to the eye also exceeds the capacity of the eye. The lower bound of concentration in the eye declines with distance, but even at the limit of the spray results in a concentration greater than 600 µg/L. The volume of fluid that could potentially be aspirated drops rapidly after 2 m due to the increase in the size of the cross-sectional area of the stream.

Table 19 presents the estimates for eye exposure for the cone spray. The approach used to evaluate the cone spray produces a single estimate of exposure. This occurs because the scenario assumes that the droplets are evenly distributed in the cone and that the individual's face and eyes are always within the cone of the spray. The data indicate that the doses to the eye are lower than those from the stream; however, the device is still predicted to deliver a dose at 5 m that results in a concentration in the eye of 300 µg/L.

Table 19. Predicted Exposures to the Eye for Cone Device at Five Distances.

Cone Spray Device					
	Distance (m)				
	1	2	3	4	5
Dose to Eye (mg)	3.9E-02	1.1E-02	1.0E-02	8.7E-03	4.8E-03
Eye conc. (µg/L)	1500	700	700	600	300

Table 20 presents the predict eye pressures for the stream and cone spray devices.

Table 20. Pressure to the Eye (psi) at Five Distances for the Stream and Cone Spray.

Device	Distance (m)				
	1	2	3	4	5
Stream	12.05	8.76	6.08	4.23	2.34
Cone Spray	10.8	6.5	4.2	3.8	1.8

The droplets from the two devices are emitted at the same velocity, but the cone spray presents lower pressures than the stream. This occurs because of the differences in droplet sizes for the two devices. Even though both devices result in large droplet sizes, the smaller droplets in the cone spray (geometric mean of 880 µm, compared with geometric mean of 1990 µm for the stream) are more affected by wind resistance than the larger droplets in the stream. As a result, the droplets in the cone spray have lower velocities and produce lower pressures.

The estimate of pressure is based on estimate of nozzle velocity for a device at room temperature. The pressure in the can and thus the nozzle velocity would be higher if the device had been stored at an elevated temperature. The size of the increase is not clear but could affect the pressure received by the eye.

5.8.2 Results for Foggers

Figure 6 presents the cumulative distribution of the sizes of the initial population of droplets and how the size and number of droplets remaining airborne change over time. As the figure indicates, the larger droplets settle out rapidly. For example, after two minutes 20% of the droplets have been removed and the largest droplets remaining airborne have dropped in size from 200 to 20 µm. Because the vast majority of the spray is contained in the larger droplets[27], more than 99.9% of the volume of the spray

[27] The volume of a droplet increase with the cube of the diameter. Thus a droplet that has a diameter that is 10 fold larger than another has a 1,000 fold larger volume.

is removed from the air in the first two minutes. The remaining 0.1%, however, is predicted to persist for much longer periods of time, with 0.03% still airborne at 20 min.

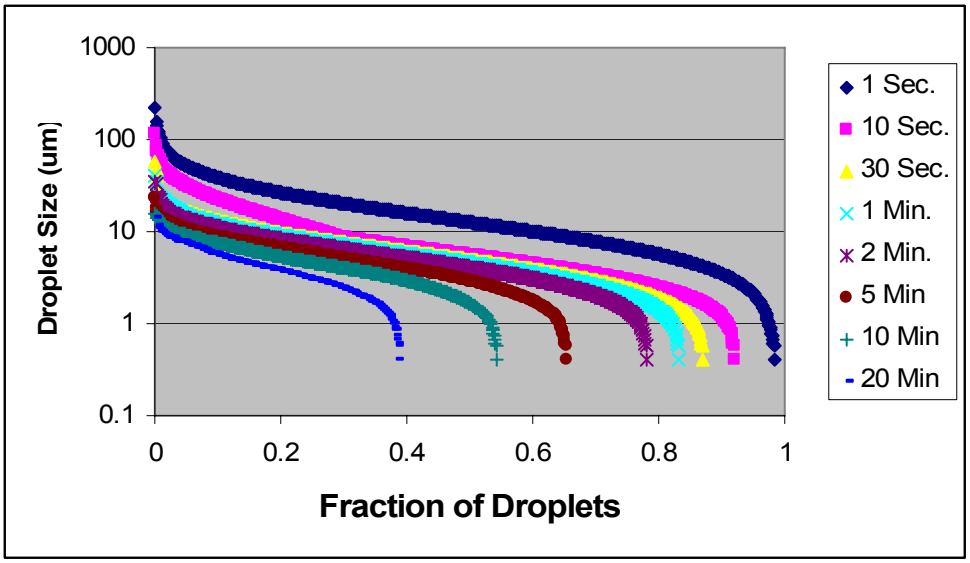

Figure 6. Distribution of Droplet Sizes in the Droplets Remaining in the Air of a Cell at Different Times after Use of a Fogger.

This small fraction of the spray volume is in the size range (<30 μm) that can be inhaled and retained in the lung. As Figure 6 shows, when 1,000 droplets are sprayed into a cell approximately 400 are initially in the range of 1-10 μm. The number of droplets in this size range remains unchanged at 20 min. This occurs because some of the larger droplets shrink and enter this range and replace the droplets that are removed by ventilation and settling. These findings suggest that a single one-second spray of a fogger can deliver relatively long exposures (>20 min) to OC aerosols in the size range that reaches the deep lung.

Table 21 presents the estimates of dose for each of three portions of the lung. The majority of the capsaicinoids are deposited in the extrathoracic region (mouth, nose, and laryngopharynx); however, the fogger delivers smaller doses to the deeper portions of the lung as well. As expected these doses tend to occur over longer periods of time than the doses to the extrathoracic portion. For example, the majority of the dose to the extrathoracic region occurs in the first 5 min. In contrast, the majority of the dose to the pulmonary portion occurs after the first 5 min of exposure.

Table 21. Doses for an Individual Remaining in a Cell for 1, 5, 10, and 20 min after Fogging.

Cumulative Deposited Doses of Capsaicinoids (μg) for Different Durations of Time After Fogging			
Time after Fogging (min)	**Extrathoracic**	**Tracheobronchial**	**Pulmonary**
1	324	18.8	3.93
5	959	63.1	16.3
10	1205	89	25
20	1513	125	41

The fogger exposure model was also used to explore the effect of changes in the amount of inert solids on inhalation exposure. The modeling suggests that the potential for inhalation exposure is increased when the level of inert solids is reduced. For example, if the fogger used a mixture with no inert solids (such as the mixture used in the Brand X and Y devices, 0.3% PAVA in a 50% ethanol solution) then the final particle remaining after the solvent has evaporated will be $(1/0.003)^{1/3}$ or 7-fold smaller in diameter than the original droplet. Yet it still delivers the same amount of capsaicinoids. Figure 7 and Table 22 presents the model predictions for a fogger delivering such a solution.

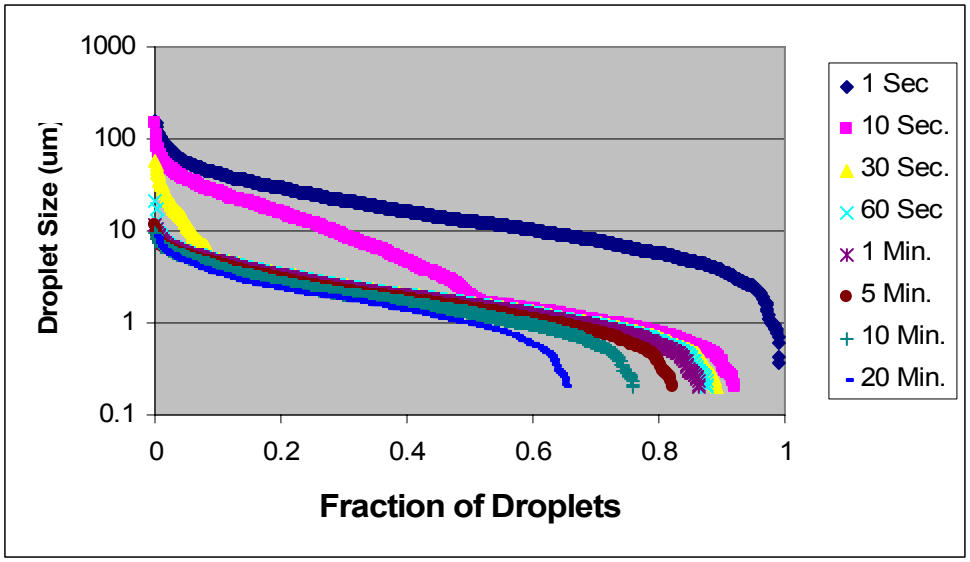

Figure 7. Distribution of Droplet Sizes in the Air of a Cell at Different Times After a Fogging using a Low Solids OC Spray.

Table 22. Dose for an Individual Remaining in a Cell for 1, 5, 10, and 20 min after Fogging with a Low Solids Spray.

Deposited Doses of Capsaicinoids (μg) for Different Durations of Time After Fogging			
Time (min)	**Extrathoracic**	**Tracheobronchial**	**Pulmonary**
1	300	42	31.7
5	1433	271	182
10	2551	492	354
20	4508	848	647

As Figure 7 indicates, more than 60% of the droplets will fall in the 1-10 μm range and will be present for more than 20 min. The doses that result from exposure to such a device are given in Table 22. As the table indicates, the doses to the tracheobronchial and pulmonary portions of the respiratory system are increased 8- and 15-fold over the spray used in the device (containing 10% solids).

5.8.3 Results for Flammability of solvents

An assessment of flammability was performed on the solvents reported by Conrad (2004) to be used in OC sprays. These solvents are isopropanol, ethanol, sec-butanol, propylene glycol, diproplyene glycol methyl ether, and d-limonene[28]. Isopropanol is the most flammable based on these combinations of properties and may be flammable at concentrations as low as 10% in water. This low level of concentration is due to the low value of the LEL for the compound (20,000 ppm v/v) its high vapor pressure (44 torr), and the fact that the thermodynamic activity coefficient is predicted to go up rather dramatically as the concentration of isopropanol goes down in water. Ethanol is predicted to be flammable down to a concentration of about 35% in water. Sec-butanol is predicted to be not flammable below 85% in water. Propylene glycol, diproplyene glycol methyl ether, and d-limonene are not flammable at room temperature even as pure materials and therefore do not present any risk of flammability. The fraction of solvent that is sufficient to support ignition will decrease at higher temperatures (summer time or if the clothing is warmed by body heat). The impact of this may be important for ethanol, isopropanol, and sec-butanol but will not affect the findings for propylene glycol, diproplyene glycol methyl ether, and d-limonene.

Based on this finding, the two PAVA products which contain 50% ethanol would be considered as being potentially flammable. As discussed above this finding does not indicate that all uses of the device where a source of ignition is present will result in a fire only that the potential for the mixture to catch fire can not be ruled out.

[28] d-limonene also has limited water solubility and is likely added with other solvents.

5.9 MODELING DIETARY DOSES

Individuals in the U.S. and other countries include chili peppers as part of their regular diet. This practice results in oral intake of large amounts of capsaicinoids. This information is useful in the OC device assessment since it provides a perspective on the oral doses of these compounds in the general public (although as noted in Section 3 the kinetics of ingestion of OC from personal defense sprays versus dietary sources may differ). Details of this assessment are provided in Appendix G. Estimating the Dietary Intake of Capsaicinoids from the Consumption of Chili Peppers and Foods Containing Chili Peppers.

In Appendix G, the daily doses of capsaicinoids are determined using a software program, LifeLine Version 3.0 (LLG, 2005). LifeLine Version 3.0 is currently used by the U.S. EPA to model dietary exposures to substances in food. The program is based on the results of a national dietary survey (BARC, 2004) that records the dietary intake of individuals. The software allows the user to enter data on the level of a substance in the agricultural commodities that are used in various types of food. The software then tracks the foods made with the commodities and the amount of the foods consumed by individuals on a given day.

The results of the analysis are given in the following figures. Figure 8 shows the variation of average daily intake with age. This intake includes all individuals, both consumer and non-consumer of chili peppers. The figure indicates that capsaicinoid intake increases with age and for adults is in the range of 0.12- 0.14 mg/kg or 8-10 mg per day. These findings appear to be reasonable since adults consume more piquant foods than do children. The distribution of doses of capsaicinoids in adults during the summer is given in Figure 9. The figure indicates that on any given day the majority of individuals do not consume foods containing capsaicinoids. However, approximately 15% of the population consumes at least one food containing capsaicinoids. In this 15% of the population, the doses range from <0.1 mg/kg to more than 10 mg/kg (or <7 to 700 mg) of capsaicinoids per day.

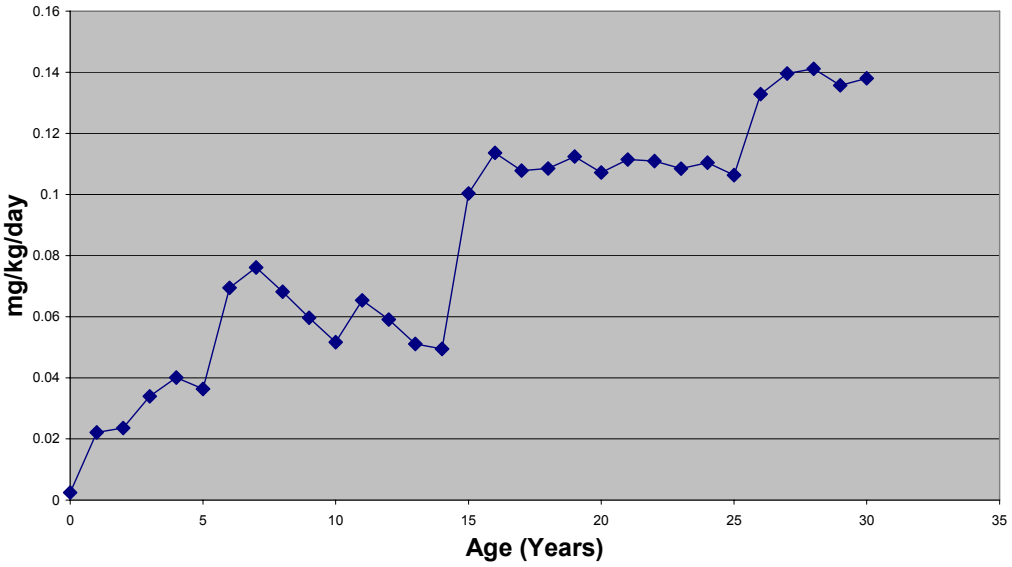

Figure 8. Average Intake of Capsaicinoids by Age in the US Population.

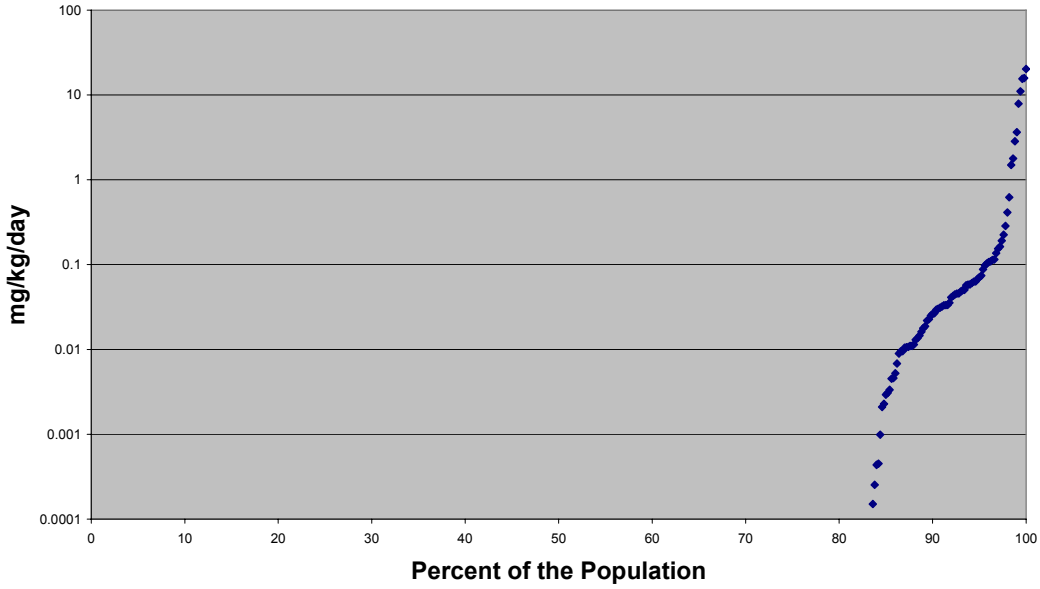

Figure 9. Distribution of Daily Intakes of Capsaicinoids in the Adult U.S. Population.

6 EFFECTIVENESS AND RISK OF OC AND PAVA

6.1 CHARACTERIZING THE OCCURRENCE OF EFFECTS

The wide range of OC- and PAVA-containing devices was evaluated by assessing three hypothetical devices and their use in two exposure scenarios. The three devices were selected to illustrate the three general types of devices, the stream, the cone spray, and the fogger. The stream and the cone sprays were assessed using a scenario where the devices were used in a one-on-one basis in an environment where wind and precipitation are not an issue (either indoors or out of doors under good weather conditions). The fogger was evaluated using a scenario of a fogger used indoors, as has been described for use in correction facilities. This scenario was selected since it presents a potential for higher exposures than other uses of a fogger.

The three illustrative devices are partially based on data from three commercially available devices. The devices were selected as the basis for the devices because they have relatively large amounts of information available, As stated in Section 5, none of the three devices have sufficient information to support an exposure assessment. As a result additional assumptions were made that may or may not be applicable to these specific products. As a result, the findings of this analysis cannot be used to make device-specific findings for OC and PAVA commercial devices. However, the assessment provides insight to risks and effectiveness of the general types of devices. In addition, the approach provides insights to characteristics of the OC devices that are associated with elevated risks.

The stream and cone spray both produce a spray that consists of large (non-inhalable) aerosol droplets, but differ in the width of the stream. The risk characterization for these devices was conducted as a function of the distance between the officer and the target, focusing on the recommended use range of 1-5 m (3.3-16 ft) for the Brands X and Y devices. The fogger is not defined in terms of distance since the fogger is used to fill a small cell with the aerosol. Results of the stream, cone spray and fogger for the various endpoints evaluated are shown in Tables 23 and 24, and discussed in the remainder of this section. The ratios shown in these tables were calculated based on the ratio between exposure for the given scenario, as calculated in Section 5, and the threshold for the effect of interest, as described in Section 4. The exception is that the threshold used for bronchospasm in healthy adults is a sub-threshold value, as described further below. In addition, the thresholds for the intended effects (tracheobronchial irritation, based on cough as a surrogate, and eye irritation) are the estimated dose at which *all* normal subjects would respond, rather than a threshold at which people begin to respond. Thus, ratios greater than 1 mean that the endpoint is expected to occur (for intended effects), or has some probability of occurring (for unintended effects). The basis for, and interpretation of these results is discussed in the remainder of Section 6.1.

Table 23. Ratio of Exposure to Threshold[a].

Spray Device					
	Distance (ft)				
Endpoint	3.3	6.6	9.8	13	16
Eye effect (Intended effect)	40	40	>30	>20	>10
Aspiration of liquid - adult	<0.04	<0.04	<0.01	<0.01	<0.003
Aspiration of liquid - child	<0.07	<0.07	<0.02	<0.01	<0.004
Pressure injury to eye – SE 1	0.6	0.4	0.3	0.2	0.1
Pressure injury to eye – SE 3	0.3	0.2	0.2	0.1	0.06

Cone Spray Device					
	Distance (ft)				
Endpoint	3.3	6.6	9.8	13	16
Eye effect (Intended effect)	30	10	10	10	6
Pressure injury to eye – SE 1	0.5	0.3	0.2	0.2	0.09
Pressure injury to eye – SE 3	0.3	0.2	0.1	0.1	0.05

[a] Ratios greater than 1 mean that the endpoint is expected to occur (for intended effects), or has some probability of occurring (for unintended effects). Ratios less than 1 are NOT associated with effects. These ratios assume that the spray reaches the target, and the ratios for the intended effect exclude individuals experiencing excited delirium.

The results for the stream and cone spray devices are summarized in Figures 10 and 11. The ratio between the intended eye effect and unintended effects (aspiration of inert liquid, pressure injury to eye) is an indication of the margin of effectiveness. Note, however, that the ratios for intended and unintended effects are not directly comparable, since the threshold used for the intended effect is based on the dose that would cause an effect in nearly all subjects, while the threshold for the unintended effects is the lowest dose estimated to cause the effect. A comparable figure is not shown for the fogger, due to the absence of an identified threshold for bronchoconstriction in healthy individuals. It is only known that the threshold is at least 1000 times the threshold for sensitive asthmatics.

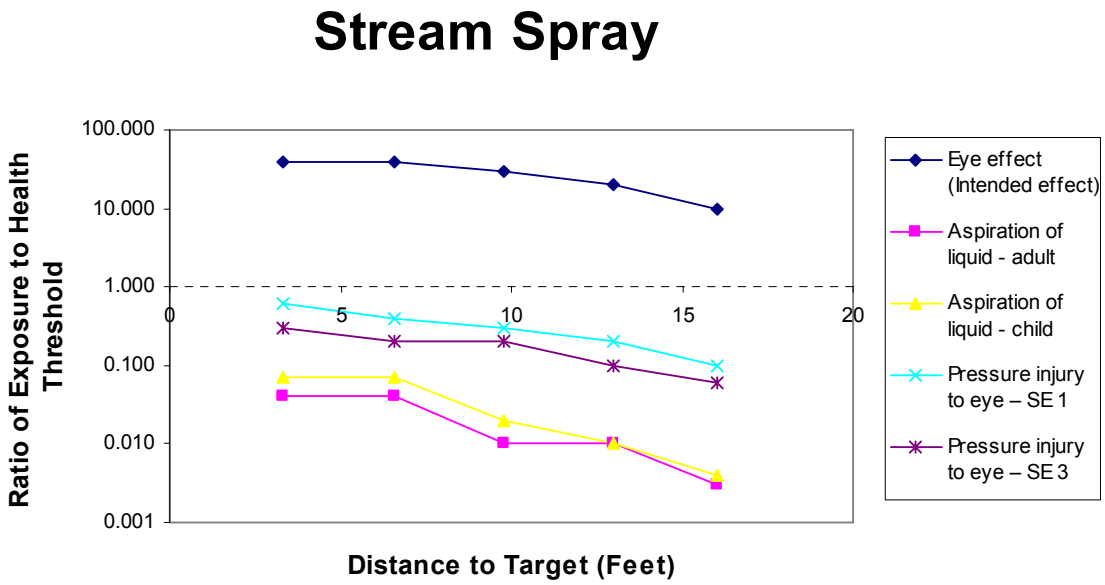

Figure 10. Summary of Ratio of Exposure to Threshold for Stream Spray Devices.

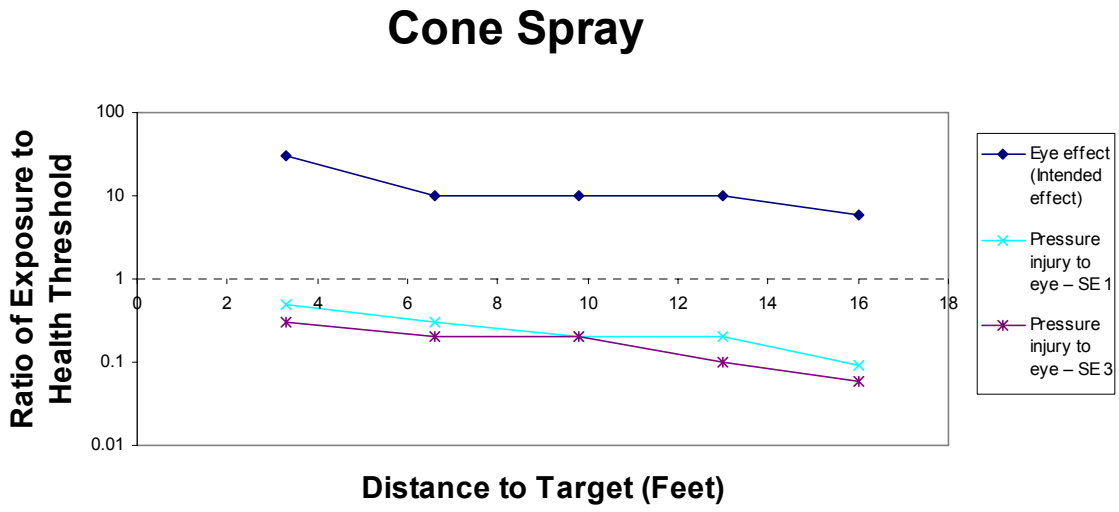

Figure 11. Summary of Ratio of Exposure to Threshold for Cone Spray Devices.

Table 24. Ratio of Exposure to Threshold[a].

Fogger				
Time (min)	**Tracheobronchial – Irritation (Cough)**	**Tracheobronchial – Bronchoconstriction in Healthy Individuals[b]**	**Pulmonary**	**Tracheobronchial – Bronchoconstriction in Sensitive Asthmatics[c]**
1	100	<1	0.3	1000
5	300	<5	1	5000
10	500	<7	2	7000
20	700	<10	3	10,000

[a]Ratios greater than 1 mean that the endpoint is expected to occur (for intended effects), or has some probability of occurring (for unintended effects). Ratios less than 1 are NOT associated with effects.
[b]Ratios are based on the assumption that healthy individuals are at least a thousand fold less sensitive than sensitive asthmatics, based on the bronchoconstriction data of Hathaway et al. (1993). This is a health-protective assumption, since that study did not find any effects in healthy individuals.
[c]Separate data on thresholds for cough in the sensitive asthmatics were not available.

As discussed in Section 5, some endpoints were considered relevant for only some of the scenarios, and therefore were presented in Tables 23 and 24 only for the relevant scenarios. The endpoints summarized in Table 25, as well as the scenarios and endpoint combinations not considered relevant are not further discussed in this section.

Table 25. Effects Not Evaluated in the Effects and Risk Characterization.

Effect	Target	Devices Not Applicable For
Eye irritation and blepharospasm	Eye	Fogger
Pressure injury from liquid stream	Eye	Fogger
Respiratory irritation	Respiratory System	Stream and cone spray*
Bronchospasm	Respiratory System	Stream and cone spray*
Pulmonary effects	Respiratory System	Stream and cone spray*
Aspiration	Mouth/Throat	Cone spray and fogger

* Some cone sprays may include respirable size droplets. If so, they could cause effects in the respiratory system.

6.1.1 Characterizing the Occurrence of Ocular Effects

For the OC and PAVA products, ocular effects (primarily blepharospasm or involuntary shutting of the eye) are desired effects; irritation and pain occur concomitantly with the desired effect. Blepharospasm was considered to be synonymous with effectiveness for this assessment. The potential for blepharospasm in the target is calculated using a threshold approach, based on the eye irritation data in animals from Jancso et al. (1968). However, as noted in Section 3, some subjects do not experience blepharospasm, and/or are not incapacitated, even after receiving eye doses that are normally incapacitating. These subjects are generally in a state of

"excited delirium," due to the effects of alcohol or drugs, and cannot be included quantitatively in the assessment. Excluding such subjects, the exposures calculated for the hypothetic stream and cone sprays indicate that PAVA delivered by these devices would be effective at all distances within the use specifications (Figures 10-11). The presented effectiveness data assume that the target was hit with the spray in a manner that resulted in droplets being deposited in the eyes. Professional judgment was used to estimate the range of doses that are likely to occur across multiple users and targets. The finding suggest that if even a small fraction of the spray mixture reaches the eyes of the target individual the intended ocular effects will occur. The current exposure model does not assess exposure to the user or bystanders. However, based on the very low threshold for eye irritation, it is prudent to assume that any contact between the spray and eyes of those individuals will be irritating. Eye effectiveness was not calculated for the fogger, because the small droplet sizes of the aerosol generated suggest minimal deposition in the eyes[29].

The assessment did not address quantitatively the potential for corneal burns due to the solvent, or the potential for corneal abrasion. For both of these effects, the risk depends on the solvent. Many different solvents are used in different OC products, several of which have the potential to cause corneal burns. (See Appendix B for more information on solvents and propellants with potential ocular effects.) Ethanol is an eye irritant, but of sufficiently low potency that corneal burns have not been reported. In the absence of a single standardized product, quantitative aspects of potential ocular effects of solvents were not investigated further. Corneal abrasions have been observed after use of OC, but the risk of this effect is determined by the solvents and propellants in the particular product. The tendency to rub one's eyes in the presence of irritation also increases the potential for corneal abrasion. Children are more likely to be affected than adults, since they may not follow instructions to avoid rubbing the eyes.

Pressure injury to the eye can occur from the force of the spray containing OC or PAVA, if the spray is used at a short distance relative to its intended use. Quantitation was based on thresholds derived from the data of Stuhmiller (1999). No pressure injuries to the eye would be expected to occur for the stream or cone spray since the estimate of the droplets at the nozzle were estimated to be 17 m/sec a value that is below the 18 m/s threshold for solvent mixture with a density of 900 kg/m^3. The similarity of the ratios of exposure to threshold for the stream and cone devices reflects the use of the same droplet velocity, and the use of the impulse pressure from individual droplets as the dose measure. At distances of 1 meter (3.3 ft) the velocity of the droplets for the stream and cone declined to 12 and 10 m/s. Pressure injuries to the eye are not expected for the fogger because these devices are not directed at the target's face, and within one meter of the nozzle, the droplets lose all kinetic energy (Appendix H).

While these results suggest that the OC devices do not pose a risk of eye penetration there are a number of factors that raise concern for this endpoint. First, the unpredictable nature of subjects precludes the complete exclusion of the use of the devices at distances of less than 1 meter. The estimated nozzle velocity of 17 m/s for

[29] While not examined in this assessment it is possible that deposition of the OC or PAVA in the sinuses could trigger tearing and eye effects. Some minimal direct deposition to the eye could also occur, but could not be accounted for in the model used.

the cone and stream devices is very close to the velocity associated with the SE 1 for eye damage (iris contraction). The margin is slightly larger for SE 3 eye effects (eye damage requiring medical attention), such as corneal damage or hemorrhage, but not sufficiently large to rule out eye effects if used at distances less than 1 meter or elevated pressures. If there is variation in pressure from one can to another it is possible that nozzle velocities in some devices will exceed the threshold of 18 m/s. In addition, storage of devices at elevated temperatures is likely to increase the pressure in the can and the velocity of the droplets. Elevated temperatures could occur in devices stored such in the trunk of a police vehicle on a hot summer day or devices exposed to direct sunlight. Finally, there are devices that are commercially available, such as Guardian Angel® (Piexon, 2004), that advertise a nozzle velocity of 40 m/s; this is almost twice the velocity necessary to cause SE 3 effects at a distance of 1 meter.

6.1.2 Characterizing the Occurrence of Respiratory Effects

Nasal irritation and pain is likely to occur from nasal exposure to OC or PAVA. It appears that any significant nasal exposure will be irritating. Because nasal effects are not incapacitating, and eye and lower respiratory tract effects are of greater concern for unintended SE 1 effects, nasal effects were not evaluated quantitatively.

Impaired respiration can be an intended effect of OC- or PAVA-based devices that create aerosols with a significant percentage of small droplets. This was considered an SE 1 effect based on tracheobronchial dose, with the threshold calculated based on the data of Doherty et al. (2000) for median concentration causing cough in normal subjects. Cough was used as a surrogate for effectiveness, in the absence of more relevant dose-response data. As shown in Table 26, exposures to the hypothetical fogger for times as short as 1 minute would be expected to cause doses almost 40 times the threshold. Therefore the product is like to be effective at inducing the desired effect for a large percentage of the population.

Bronchoconstriction is an unintended effect. Individuals with asthma or cardiopulmonary disease have an elevated risk for this effect. Bronchospasm was evaluated separately for normal individuals and asthmatics. No good threshold data were identified for bronchoconstriction in normal subjects; Hathaway et al. (1993) reported that no bronchoconstriction occurred at the highest concentration tested, 1000 times the no effect level in a sensitive asthmatics. One study (Blanc et al., 1991) reported bronchoconstriction in one capsicum worker following challenge with a dose lower than the threshold identified for asthmatics. This person did not have a history of asthma treatment, but undiagnosed asthma cannot be ruled out, and this study generally found thresholds for healthy subjects at much lower concentrations than those in other studies. No other reports of bronchoconstriction in healthy subjects were located, although most studies only tested up to deposited doses in the range of those causing bronchoconstriction in the sensitive asthmatics. Because no testing was done at doses that caused bronchoconstriction in the healthy subjects, no effect level can be identified for them. Therefore, the ratios (of dose to threshold) for bronchoconstriction in healthy people shown in Table 26 are reported as greater than some value. Based on these results, there may be some risk for bronchoconstriction in healthy individuals, but this potential could not be quantified. This potential could be better quantified by monitoring of bronchoconstriction after use of fogger devices.

The potential for bronchoconstriction in sensitive asthmatics was based on the lowest effect level identified in a study of asthmatics exposed to nebulized OC (Hathaway et al., 1993). The threshold for this effect is a particular concern since it is approximately an order of magnitude lower than the threshold for the desired effect. This implies that any effective OC-based fogger device would pose some risk of bronchoconstriction to sensitive asthmatics. However, based on the data indicating that asthmatics have a lower cough threshold than healthy individuals, it is expected that cough would occur before bronchoconstriction for any individual. No comparative data on cough vs. bronchoconstriction was available for the sensitive asthmatics that experienced bronchoconstriction.

As discussed further in Section 6.3, the threshold for individual asthmatics tested in the Hathaway et al. (1993) study varied by several orders of magnitude. In addition, while the bronchoconstriction observed at doses above the threshold was clinically significant, it would not necessarily require medical attention. Therefore, it is not known whether all asthmatics would be affected in the baseline scenario, and, if so, the severity of response. As shown in Table 26, exposures as short as 1 minute would be expected to exceed the threshold for bronchoconstriction in sensitive asthmatics in the baseline fogger scenario.

Pulmonary effects, including inflammation, edema, hemorrhage, and alveolar emphysema, have been reported in an animal study that evaluated histopathological effects of OC and PAVA exposure; less severe pulmonary effects have been reported in people at high exposures (Olajos & Salem, 2001). This animal study was reported in the paper of Reilly et al. (2003a), supplemented by data in Crouch et al. (2003) and other personal communications from G. Yost (October 26, 2004 and November 5, 2004), and the occurrence of pulmonary effects was evaluated based on threshold data derived from these sources. As shown in Table 26, there may be a risk of pulmonary effects under the fogger scenarios; the data are not sufficient to translate this potential into a probability of an effect. Although the ratios exceed 1 for durations of 5 min and longer, there is sufficient uncertainty in the threshold that the percentage of the population that would be affected at these doses is unclear.

One of the key findings in the exposure assessment is identification of the potential for droplets to lose their solvents during the time that they are airborne. This finding suggests that aerosols that initially have a limited potential to reach the deep lung due to their large size could in fact reach the lung after the solvent has evaporated. For the mixture used in the hypothetical analysis of the fogger, the droplets can decrease their size by a factor of two within two minutes. Such shrinkage can increase the probability that a droplet is deposited in the deep lung by a factor of 10. However, the degree of shrinkage in this product is limited by the high level of solids in the spray mixture. Thus, for example for the Brand Z Fogger, the total amount of capsaicinoids in the solvent is 0.33% but the total amount of the OC is 10% (9.67% inert solids and 0.33% capsaicinoids). Thus, the removal of the solvent can result in a maximum 10-fold reduction in volume, or slightly more than a 2-fold reduction in diameter. If the inert solids in the mixture were lower, then degree of shrinkage would be higher.

To test the impact of a reduction in solids the analysis was rerun with the assumption that there were no solids and 0.3% capsaicinoids. The droplets would be

99.7% solvent and water. The shrinkage factor would be 333 and the reduction in the diameter of the droplets would be 7 fold. The results are presented in Table 26.

Table 26. Ratio of Exposure to Threshold for a Low Solids Fogger[a].

Fogger – Low Solids Spray				
Time (min)	Tracheobronchial – Irritation	Tracheobronchial – Bronchoconstriction in Sensitive Asthmatics	Tracheobronchial – Bronchospasm in Healthy Individuals[b]	Pulmonary
1	200	3,000	<3	2
5	1,000	20,000	<20	10
10	3,000	40,000	<40	20
20	5,000	70,000	<70	40

[a]Ratios greater than 1 mean that the endpoint is expected to occur (for intended effects), or has some probability of occurring (for unintended effects). Ratios less than 1 are NOT associated with effects.
[b]Ratios are based on the assumption that healthy individuals are at least a thousand fold less sensitive than sensitive asthmatics.

As discussed in the exposure section of this report, the low solid fogger delivers doses to the deep lung that are 8- to 15-fold higher than those delivered by a fogger with percent solids comparable to the Brand Z fogger product. These higher doses greatly increase the risk of pulmonary effects.

While the exposure assessment determined that hypothetical devices evaluated, producing large aerosol droplets, would not have droplets small enough to be inhaled or affect the respiratory tract, the possibility of some respiratory tract irritation cannot be ruled out for other devices producing large droplets. For example, a stream of large droplets may have a tail of fine aerosols. While these droplets would constitute a small percentage of the total released materials, they may be sufficient to cause some respiratory irritation. In addition, the use of a large-droplet aerosol indoors can lead to the production of finer droplets, from such processes as droplet bounce-back, evaporation, and re-entrainment.

If the target is inhaling with an open mouth when the stream of OC or PAVA strikes the mouth, liquid may be aspirated into the lungs. The potential for the occurrence of adverse (SE 2) effects from liquid aspiration was estimated based on the data of Schmidt and Madea (1995) and Fiore and Heidemann (2004), who reported aspiration volumes of inert liquids that could cause pulmonary effects. Based on these data, pulmonary effects from aspiration of an inert liquid do not pose a risk to adults or children exposed to the stream or cone spray.

Note, however, that this threshold is for aspiration of an inert liquid. Aspiration of OC or PAVA would deliver an irritating agent directly to the pulmonary tissue. The potential for pulmonary effects from aspiration of the agent depends on the actual volume within the estimated range that is aspirated[30]. Based on the rarity of reports of breathing difficulty not related to laryngospasm or bronchospasm, aspiration events leading to pulmonary effects appear to be rare. A possible reason for the rarity of

[30] This conclusion is based on an estimated volume delivered to the mouth at the closest distance of 0.01 – 0.3 mL. For a 0.3% PAVA solution, a dose of 0.01 mL would result in an aspirated amount of 30 μg, well above the threshold of 4 μg estimated for pulmonary effects.

aspiration events is that the estimate of aspirated volume provides is the amount of liquid that *could* be aspirated if the stream hits the mouth and the mouth is open. As discussed in the exposure section, whether that volume is actually aspirated into the lungs depends on a number of complex factors beyond this assessment, including the angle of the head, how wide open the mouth and throat are, whether the target is inhaling at the moment of impact, and whether the droplets hitting the mouth stick to the back of the throat or pass the epiglottis to enter the lungs. In light of the absent or minimal risks from the stream, the volume delivered to the mouth from the cone spray was not modeled. This volume would be much less than for the stream, based on the dispersal characteristics of the cone spray.

Furthermore, no reports of such effects were located in the literature, although the absence of a systematic reporting system means that the possibility of a few cases worldwide cannot be ruled out. OC devices vary markedly in the operating instructions provided. However, the approach recommended by the manufacturer of the PAVA device used for the illustrative characterization is to aim for the forehead. The manufacturer states that this allows the spray to drip into the eyes; this approach would also minimize the potential for eye pressure injuries and liquid aspiration.

6.1.3 Characterizing the Occurrence of Skin Effects

Skin irritation is likely to occur from dermal exposure to OC or PAVA. Skin irritation could also occur from prolonged exposure to ethanol, but such exposure is unlikely, particularly in light of the strong irritation from the capsaicinoids. Because skin effects are not incapacitating, and eye and lower respiratory tract effects are of greater concern for unintended SE 1 effects, skin effects were not evaluated quantitatively. It is reasonable to assume that any “significant” exposure of the skin (functionally defined by direct impact of the spray or fog) will induce a pain effect. Skin sensitization is unlikely to occur.

6.1.4 Characterizing the Occurrence of Ignition

Use of OC-based products creates aerosols of flammable solvent and the application of flammable solvents to individuals. The potential for ignition of the solvent was evaluated based on a model of the saturated air concentration of the solvent from the solvent mixture in the specific preparation of OC or PAVA, and the lower explosive limit for the flammable solvent in the mixture used. A solvent was assumed to be flammable when the vapors of the solvent above the solution are capable of reaching the Lower Explosive Limit (LEL) concentration. Among the solvents commonly used for OC and PAVA, isopropanol is the most flammable. Ethanol is predicted to be flammable down to about 35% concentration in water. This suggests that the PAVA products (dissolved in 50% ethanol in water) will be flammable. Sec-butanol is predicted not to be flammable below about 85% in water. Propylene glycol, diproplyene glycol methyl ether, and d-limonene are not flammable at room temperature even as pure materials and therefore do not present a risk of flammability. The fraction of solvent that is sufficient to support ignition will decrease at higher temperatures (summer time or if the clothing is warmed by body heat). The impact of this may be

important for ethanol, isopropanol, and sec-butanol but will not affect the findings for propylene glycol, diproplyene glycol methyl ether, and d-limonene. Based on this finding, the two PAVA products which contain 50% ethanol would be considered as being potentially flammable. As discussed above, this finding does not indicate that all uses of the device where a source of ignition is present will result in a fire, only that the potential for the mixture to catch fire can not be ruled out.

6.1.5 Characterizing the Occurrence of Other Effects

A number of other potential effects were identified, but were not evaluated further, as discussed in the summary section of Section 3 (Table 10). Insufficient data were available to evaluate the potential for cardiovascular effects, risk of increased intraocular pressure, reactive airway dysfunction syndrome (RADS), neurotoxicity, and developmental or reproductive effects. Developmental effects (particularly neurodevelopmental effects) and reproductive effects are of potential concern, and represent a significant data gap. Increased blood pressure that is likely to be secondary to pain was considered to be of concern for certain populations, but was not evaluated due to the absence of sufficient quantitative data. Similarly, extrapolation from other irritants indicates that increased intraocular pressure is of concern for sensitive populations (e.g., those with glaucoma), and RADS is of concern for the general population at sufficiently high exposure concentrations, but these endpoints were not evaluated due to the absence of data on these effects following exposure to capsaicinoids. Other effects considered but not fully evaluated were GI irritation (relatively low health consequence, inadequate data to quantify); thermoregulatory effects (low health consequence); effects on the liver, kidney, or other target organs (inadequate data to quantify, but exposures unlikely to exceed threshold for moderate or severe effects); immunotoxicity (inadequate data to quantify); and cancer (very low probability based on inconclusive effects data and expected exposure patterns). Acute exposure to ethanol can cause neurological effects, but evaluation of typical doses from use of these devices suggests that this effect would not occur following use of typical OC or PAVA devices. The potential for an increased risk of in-custody deaths was also considered but not quantified. Although most in-custody deaths have not been associated with the capsaicinoid exposure, a small increased risk was identified, primarily for people with severe asthma or other pulmonary dysfunction exposed to the small aerosol droplet sizes, as described above in Section 6.1.2.

6.1.6 Resistant Populations

While this assessment has focused on effects and effectiveness in normal individuals, OC and PAVA devices may be used on people under the influence of drugs or alcohol. As discussed in Section 3, people under such influence may exhibit “excited delirium,” and be resistant to the irritant and/or incapacitating effects of these devices. The degree of resistance could not be further quantitated.

6.1.7 Sensitive Populations

As discussed in the context of respiratory effects, asthmatics and other people with respiratory disease (e.g., chronic obstructive pulmonary disease – COPD and other reactive airway disease, including asthma) are likely to have increased sensitivity to the bronchoconstriction that can be caused by capsaicinoids in the form of fine aerosols. In light of this potential it may be important to have medical backup when foggers are used on difficult individuals in enclosed spaces. Severe asthma attacks can be life-threatening, but medical treatments for asthma attacks are well known. If a severe asthma attack occurs it should be immediately treated.

Other potential sensitive populations can be identified based on physiological responses, some of which are reflex in nature, that have been observed with capsaicinoids or other sensory irritants. People with certain established diseases may also constitute sensitive populations, since exposure to sensory irritants may result in adverse effects from secondary responses (complications) to either the irritant toxicity or the physiological responses produced. These responses include transient increases in systolic and diastolic blood pressure, bradycardia, stimulation of respiratory tract receptors, severe eye pain, and transient increases of intraocular pressure. Thus, people with coronary artery disease, myocardial ischemia, cardiac arrhythmias, essential hypertension, and arterial aneurysm are at increased risk from the transient increases in systolic and diastolic blood pressure and bradycardia. People with glaucoma are at increased risk from the transient increases in intraocular pressure seen with other sensory irritants (but for which no data on capsaicinoids exists).

6.1.8 Effects in Children

Children were noted as a potential sensitive population for corneal abrasions resulting from rubbing their eyes, because they may not follow directions to avoid rubbing. Children also often have more sensitive skin than adults, and so may be more sensitive to the skin irritation effects of capsaicinoids. Since children generally consume less hot food, tachyphylaxis from consumption of capsaicinoids would not provide any protection. As mentioned above, newborns are of particular concern for neurodevelopmental effects, but no information was located to indicate whether children older than newborns would be more sensitive to neurological effects. No information was located regarding whether children are more sensitive to respiratory effects of capsaicinoids. Differences in deposited dose would depend on differences in such factors as the surface area, breathing rate, and respiratory tract geometry in the child versus adult.

6.2 Effectiveness and Risk Evaluations of OC and PAVA Developed by Other Organizations

A number of organizations have evaluated the risk of the use of OC, “pepper spray,” or PAVA. These evaluations were generally qualitative, based primarily on reported effects. Some included an evaluation of potential effects, based on the overall

database, but none to our knowledge have conducted a full quantitative risk characterization, taking exposure into account.

Busker and Van Helden (1998) reviewed the toxicological implications of "pepper spray" for use by the Dutch police and concluded that "the risk of long-term health effects is negligible" (p. 309). However, respiratory effects were noted as an area of emphasis, based on the reported case of an in-custody death of an asthmatic that was causally attributed to OC exposure. They noted that, although Blanc et al. (1991) found decreased threshold for cough induction in chili pepper workers without an effect on lung function or the frequency of asthmatic attacks, the data are insufficient for sound conclusions regarding effects on asthmatics or people with chronic obstructive pulmonary disease.

In a study by the Federal Bureau of Investigations (FBI) reviewing the effects of OC following exposures during training exercises (Weaver & Jett, 1989), it was concluded that the use of OC is "safe." Numerous signs of irritation, ranging up to shortness of breath due to bronchoconstriction, were reported, but there were no cases of damage to the eyes, skin rash, or blister formation. Other transient effects included short-term nausea, and temporary loss of upper body motor skills (e.g., decreased hand-eye coordination).

The New York State Department of Public Health conducted a comparative review of riot control agents used as personal defense sprays (Recer et al., 2002). This review concluded that OC was the safest of the available sprays. This decision has been codified in a rule promulgated by the department that specifies OC as the only active ingredient allowed to be sold and used in personal defense sprays in the State. Results of the comparative analysis are described further in Section 6.4 below.

In a review of riot control agents, Olajos and Salem (2001) concluded that "riot control agents are safe when used as intended" (p. 355), but noted concerns and data gaps regarding the effects of repeated and prolonged use.

Smith and Stopford (1999) reported that many police departments consider OC to be safe, but they noted the potential for severe effects, particularly in people with asthma. They recommended that the practice of spraying trainees directly in the face be avoided, due to the potential for effects from repetitive exposure. They also recommended that people with an increased risk of adverse effects (e.g., those with corneal disease, hypertension, heart disease, respiratory infections, bronchitis, asthma, or a history of airway reactivity after irritant exposures) be exempt from such exposures. They stated that the Consumer Product Safety Commission (CPSC) regulates the labeling of OC spray as a hazardous substance under the Federal Hazardous Substance Act. Safety recommendations for use of OC in training exercises were also provided.

Crane (1997) conducted a review of OC for the New Zealand Police National Headquarters. Crane identified a number of data gaps regarding specifications for OC formulations and health effects of exposure. Many of these gaps have been filled by studies reviewed in this HERC; others are noted in the discussion of data gaps in Section 6.3. The primary health concern in the review was the potential for respiratory effects in sensitive individuals.

In a 1993 evaluation for the State of California, DiBartolomeis et al. (1993) noted a number of data gaps for OC, particularly with regard to irreversible ocular, nervous

system, and teratogenic effects. The assessment concluded that significant undesirable effects from OC use had not been observed in other states. Also, the author expressed that usage of OC-based tear gas appears to offer a better alternative to a greater level of force (e.g., use of a police baton) or to other available tear gas weapons. Further user information from the state indicated that use of OC went forward without restrictions or follow-up evaluation, based on the consideration that effects would be less severe than those from a firearm.

The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment completed its evaluation of PAVA in November, 2004 (COT, 2004). The evaluation concluded that there are no concerns regarding skin or eye irritant effects, or developmental toxicity of PAVA (based in part on a rough conservative estimate of systemic dose), and that PAVA is not a skin sensitizing agent or *in vivo* mutagen. The committee also concluded that PAVA is unlikely to cause adverse respiratory effects in healthy individuals, but that respiratory effects may occur in asthmatics. Based on these results, the committee concluded that "low exposures arising from the use of PAVA incapacitant spray would not be expected to be associated with any significant adverse health effects. However, we recommend that monitoring of experience-in-use be continued" (COT, 2004, p. 3).

COT (2002) reported that the bulk of the droplets for PAVA were over 100 μm and that it is likely that a small proportion (1-2%) fall in the size range of 2-10 μm with a possibility of traces below 2 μm. More important the committee states that "it is unlikely that large amounts of PAVA will reach the respiratory system, although the possibility of some reaching the lungs cannot be excluded. It is not possible to estimate the respirable dose" (p. 1). No reference was provided for this determination. As discussed below, this study suffers from a number of limitations. However, most of these limitations result in a bias of the data towards *overestimating* the fraction of droplets that are less than 500 μm. Thus, the findings of this report do provide support to the conclusion that the product does not produce significant levels of respirable aerosols.

A recent comparison of CS and PAVA has also been published by the U.K. Home Office Scientific Development Branch (HOSDB) ((previously known as the Police Scientific Development Branch (PSDB)) (2004). The report summarizes the relevant effects and operational data for PAVA. The report cites the conclusions from the Committee on Toxicology report (COT, 2004) described above as supporting the use of PAVA "in the current formulations by UK police providing the guidelines for use are adhered to" (Home Office Scientific Development Branch, 2004, p. iii). Key operational findings drawn from interviews with users and reports of field uses were presented. With regard to its effectiveness, eye closure and pain were noted as the primary method of operation. The effect was described as all or nothing in most cases, having a very high effectiveness rate. Some cases were noted of a belligerent being able to continue a struggle (albeit without being able to see), and becoming even more aggressive where PAVA exposure did not incapacitate the subject. Cases of failure to have an effect on subjects who were under the influence of alcohol were noted. The effects were described as instantaneous once PAVA got into the eyes of the subject. The typical duration of the eye effects was not noted, although they were described as longer than those of CS. A key advantage of PAVA was the decreased probability of cross-contamination. For this reason, the report identified advantages of PAVA over

agents such as CS as being the better suitability of the PAVA device in confined spaces, in reducing the potential for effects on bystanders or police officers, and for reduced requirements for decontamination of equipment.

6.3 DATA GAPS, UNCERTAINTIES AND RESEARCH NEEDS

6.3.1 Effects Identification and Dose-Response

6.3.1.1 General Issues Related to Effectiveness and Effects

This HERC was developed for OC and PAVA, using data on capsaicin to supplement identified data gaps. Although the possibility of having separate thresholds for OC and PAVA was considered, the limited data comparing the two was insufficient to identify a clear difference in potency. Therefore, the same thresholds were identified for both chemicals, based on the overall best available data for each endpoint. In addition, much of the available effects data, particularly for respiratory effects, were only available for capsaicin, the best studied capsaicinoid and the primary component of most OC mixtures. However, some studies do suggest differences in potency between PAVA and capsaicin, the primary component in most OC mixtures. Studies conducting systematic comparisons of the dose-response for PAVA, capsaicin, and dihydrocapsaicin would be useful in order to evaluate the relative potency of these chemicals. These data could then be used to develop potency estimates for different formulations of OC. However, unless the OC formulation is itself standardized (e.g., based on percent capsaicinoids, or SHU, something that is done by a few manufacturers), relative potency information would not be generally useful in developing thresholds for OC, although it could help inform the development of improved thresholds for PAVA.

A primary uncertainty in the assessment was the lack of a generally agreed-upon definition of effectiveness for the aerosols containing small droplets. While incapacitation due to blepharospasm was the measure of effectiveness for the large aerosol droplet sizes, effectiveness for products producing smaller droplets was defined by using vague terms that were not directly connected to physiology, such as improved ease of arrest (Kaminsky et al., 1999). In addition, dose-response information directly related to incapacitation from small aerosol droplet sizes was not available, and so cough (a measure of respiratory tract irritation) was used as a surrogate. While several studies have been conducted on effects and effectiveness of OC products, these studies often lack sufficient information on the extent of evaluation of effects. More importantly, information on the aerosol droplet size (a key determinant of effects) was never provided in these studies, and sufficient information on the amount of OC released was usually not provided, precluding calculations of the dose or amount of exposure.

To address this issue, it would be useful to implement a systematic statistically rigorous reporting system to measure effectiveness and adverse effects. As part of such a system, one would need unambiguous and uniform definitions of effectiveness, and criteria for measuring incapacitating effects. This system would provide information on the use, including events leading up to the use or non-use (e.g., compliance

achieved from the sound of the velcro releasing the device), effects evaluated, effects observed, and information on the use conditions (type of spray, distance, where the spray hit). Alternatively, given the potentially burdensome reporting requirements associated with developing such a database, a first step would be to require OC spray manufacturers to provide information on droplet size of the aerosol released by their devices. This information could be coupled with more limited studies of effectiveness and effects under various conditions. Because corrections facilities have a relatively steady population that may be exposed repeatedly, they may be a source of data on the potential for tolerance, as well as the effects of repeated exposures and long-term effects. User data also described decreased effectiveness at lower temperatures, but data were insufficient to quantify this effect.

The final, but significant, general data gap for this assessment is absence of adequate data on any of the wide diversity of OC and "pepper spray" products on the market. This assessment was unable to identify any product which had sufficient information to allow a complete exposure and risk characterization. In addition, many devices in commercial use do not provide information on key determinants of effectiveness and risk such as identification of the solvent, propellant, concentration of capsaicinoids, and the particle size. Finally, even when information is provided, key aspects (e.g., capsaicinoid composition) are often not standardized, and vary from batch to batch of the same product.

Consideration of all formulation constituents and the total formulation itself is necessary for a complete exposure and risk characterization. It would also be useful for manufacturers to provide such information to health care providers to aid in the provision of first-aid and medical management of exposed individuals. This issue could be addressed by the manufacturer producing and making generally available to health care providers and Poison Control Centers a Material Safety Data Sheet (MSDS) for their product.

6.3.1.2 Ocular Effects

There is considerable uncertainty regarding the effective and irritating dose for ocular effects, both for capsaicinoids and ethanol. Few studies have been done to further evaluate this endpoint, at least partially due to concerns about animal cruelty in exposing animals to the very irritating agent. While this is an area of considerable uncertainty, further research in this area is not recommended for this HERC, because the data are adequate to define effective and irritant doses sufficiently for characterizing the effects from reasonable use scenarios.

A more important gap relates to the potential for ocular effects from other solvents or propellants used in the OC preparation. Many of these can cause ocular irritation, corneal burns, or corneal abrasion (compounded by the effect of rubbing the eyes). Due to the wide variability in solvents used and solvent concentrations, effects of the solvents (other than ethanol) were not evaluated in this HERC. In addition, the potential for permanent vision impairment from use of OC is low, based on the rarity of this effect after tens of thousands of uses, but insufficient data are available to evaluate this potential quantitatively. An additional uncertainty is related to the effects on contact lens wearers. SE 2 ocular effects have not been reported at an increased rate in contact lens wearers exposed to OC or PAVA, but the degree of evaluation of this issue

is not clear. Common practice often includes removal of contact lenses after exposure during field uses and flushing of the eyes; these practices would reduce the potential risk, and are recommended by this report, particularly in light of the potential for some solvents to disintegrate soft lenses. Furthermore, removal of contact lenses prior to exposure during training exercises has been recommended by some investigators

A key uncertainty for evaluating the potential for pressure injuries to the eye is the identification of a predictive dose metric that applies to water droplets emitted from a variety of devices. While the data of Stuhmiller (1999) provide some dose-response information, the variability in the data (Figure 2) suggest that there may be some additional factors affecting response not accounted for by the dose metric that was used. In addition, it would be useful to have the Stuhmiller (1999) work in the form of a peer-reviewed publication, rather than as an unpublished presentation, as well as verification from an independent laboratory.

An additional limitation to the Stuhmiller (1999) study is the inability to determine the effects from multiple droplets hitting the same portion of the eye during short time periods. The equations used in this analysis address the risk for single droplets. In the case of cone sprays, several hundred droplets could strike the eye, and several thousand droplets could strike the eye from a stream device.

6.3.1.3 Respiratory

While some dose-response data are available for nasal effects of OC, a number of different thresholds were identified for different nasal effects. Because the responses were of varying severity but unclear adversity, the appropriate response to use for the threshold was unclear. However this was not a limitation to the HERC, because a qualitative approach was used to evaluate nasal effects, as described above.

A number of important uncertainties were identified for the other respiratory effects (Table 27). For the cough endpoint used as a surrogate for respiratory irritation, the desired threshold is one that affects virtually all of the population. The threshold identified in the key study (Doherty et al., 2000) corresponded to a response of approximately 45% in normal subjects, but corresponded to 100% response in another well-done study (Midgren et al., 1992). Based on the slope of the dose-response curve, the actual threshold for affecting nearly all of the population could be as much as perhaps twice the threshold dose used in this assessment.

Other uncertainties related to the calculation of dose to the respiratory regions are discussed in Table 27. Primary among those uncertainties was the identification of the aerosol droplet size distribution (expressed as the mass median aerodynamic diameter [MMAD] and geometric standard deviation [GSD] when no data or only ranges were provided. Assuming that nebulizers are generally similar, an MMAD of 3 μm and a GSD of 3 μm were assumed in the absence of data. However, relatively small differences in the size distribution within the range reported for the nebulizer studies can affect the deposition fraction by as much as a factor of 2 or 3. Calculation of an estimated GSD based on range data tended to result in higher estimates of pulmonary dose and lower estimates of tracheobronchial dose, compared to the default. However, the implications of use of the default could go in either direction. Other uncertainties relate to the amount of material delivered (nebulizer flow rate and duration of inhalation in single-breath studies), and the volume inhaled in single-breath studies. However,

sensitivity analyses indicated that these uncertainties had a smaller effect on the estimate of deposited dose than the uncertainty regarding aerosol droplet size.

Table 27. Uncertainties in Calculation of Respiratory Tract Dose.

Uncertainty	Impact
Estimated aerosol droplet size as MMAD = 3 μm, GSD = 3 μm when not reported	Not known
Using the regional deposited dose as the dose metric	Not known
Assumption that the entire nebulized amount was inhaled	Overestimates the dose to both regions
Extrapolation from concentration in solution using the data of Midgren et al. (1992)	Not known
Not addressing the impact of cough on deposited dose	Overestimates deposited dose
Assumption that cough is determined by the tracheobronchial dose, rather than the extrathoracic dose	Implication depends on width of aerosol droplet sizes distribution. Minimal effect for wide distributions; lowers estimate of dose for tighter distributions

One of the biggest uncertainties in the estimation of deposited dose for the evaluation of dose-response was in extrapolating from the capsaicin concentration in solution to the inhaled amount (and from there to dose to the respiratory tract). When the volume nebulized was reported, it was assumed that the entire nebulized volume was inhaled, due to small dead space in the apparatus. This was a reasonable assumption in the absence of better data, but would result in an overestimate of the inhaled amount. When the nebulized amount was not reported, it was assumed that the volume nebulized was the same as in the one study of similar design where it was reported (Midgren et al., 1992). The implication of this assumption is not known.

Cough (as a surrogate for a measure of effectiveness) was considered to be a tracheobronchial effect. As discussed in Section 3, this effect can result from exposure of the head (larynx), and tracheobronchial regions. The assessment could be enhanced by using a dose metric that takes the dose to both of these regions account, although any implications of high doses in only one region (e.g., only the tracheobronchial region) could be lost by only using such an approach. For the default, relatively wide aerosol droplet size distribution, deposited dose to the tracheobronchial and head regions would be comparable, so the choice of target region would not affect the threshold. For tighter distributions estimated for some of the studies, dose to the tracheobronchial region is lower than the dose to the head region, so assuming that the effect is due to the tracheobronchial dose results in a lower estimate of the threshold. On the other hand, any coughing by the test subject during the inhalation period was not accounted for in the dose estimate, but would decrease the deposited dose. This would mean that the threshold was over-estimated. Finally, the approach used also assumed that the deposited dose (taking into account duration of exposure) in the respiratory tract region

is the correct dose metric. This is a reasonable assumption based on the available mechanistic data on aerosol exposures, but the inconsistency between thresholds estimated from different studies suggests that neither concentration in the aerosol nor deposited dose fully explain the observed dose-response.

Other uncertainties regarding the respiratory effects relate to the dose-response assessment. While the incapacitating aspect of respiratory irritation is laryngospasm (temporary paralysis of the larynx with associated gasping and gagging), no dose-response information was identified specifically for this endpoint, and cough was used as a reasonable surrogate. Laryngospasm is usually of short duration (Crane, 1997). A primary uncertainty is related to the fact that the dose estimated as a threshold for bronchoconstriction in sensitive asthmatics is lower than the dose estimated as a threshold for cough in a high percentage of the population (as a surrogate for incapacitation). Much of the difference between these two thresholds relates to the increased sensitivity of asthmatics compared to the normal subjects; asthmatics also appear to have higher sensitivity to cough than normal subjects. As described in Section 4, the threshold for bronchoconstriction is based on the no effect level for the most sensitive asthmatic subject in the Hathaway et al. (1993) study. Of 17 asthmatics, only seven showed any bronchoconstriction at any dose, with only three exhibiting a clinically significant change (>20% decrease in FEV_1), two at doses at least 10x that causing the effect in the most sensitive subject. No bronchoconstriction was seen in any normal subjects up to the highest dose tested (0.3 mg/mL capsaicin in solution; or 1000 times the no effect level in asthmatics). This estimate is a lower bound, and the actual threshold is not known. Thus, there appears to be a tremendous amount of variability in sensitivity to the bronchoconstriction effects of capsaicin. Note also that the threshold is based on clinically significant bronchoconstriction, but the severity of the effect at the threshold is such that it could be readily treated, or may resolve without treatment. Increased use of products that generate large aerosol droplet sizes would shift the intended effect to ocular impacts, and would reduce emphasis on the need to resolve this important uncertainty. This conclusion is similar to the comments of Crane (1997) in recommending a choice of technologies that generate liquid streams, as well as COT (2004) with regard to concern about asthmatics.

The bronchoconstriction threshold is based on a sensitive asthmatic while the selected threshold for cough may be well above the actual threshold for most individuals. Therefore, the low bronchoconstriction threshold is not inconsistent with the rarity of bronchoconstriction events or asthmatic attacks under conditions of effective OC use. Conversely, someone with severe asthma or even severe airway hyperresponsiveness (which may be present without obvious asthma symptoms) might have a lower threshold for bronchoconstriction than the value used in this assessment; more severe effects might also occur in these people at doses in the range of the effectiveness threshold. Crane (1997) reported that even the act of coughing can induce transient bronchoconstriction in sensitive individuals, and suggested that this risk would increase in the presence of pain and fear occurring in police confrontation situation. Air pollution can affect breathing, and may also affect the respiratory effects of OC or PAVA sprays of small aerosol droplet size.

No data were available regarding the respiratory effects of repeated exposure to OC or PAVA sprays. Occupational exposures to OC in pepper and spice manufacturing

have identified decreased respiratory function in several studies (reviewed in Stopford, 2004), but information on droplet size of the aerosol or dust was insufficient to calculate respiratory tract dose. This is of particular concern in light of the potential for repeated exposures (of users, and of people in correction facilities), and in light of the estimate that doses that can cause bronchoconstriction in sensitive individuals may be lower than respiratory doses that cause coughing (as a surrogate for incapacitation) in a high percentage of the population. No information was found regarding monitoring of respiratory effects in corrections facilities; the only study from such facilities (Brown et al., 2000) only evaluated ocular effects. Users would tend to have a lower exposure than the target, but would have potential exposure from either blow-back of the spray (e.g., due to wind), or because they moved into the droplet cloud in order to apprehend the target. It is reassuring that no studies of police officers using OC have reported bronchoconstriction in the users, but it is unclear whether this endpoint was fully evaluated.

Another potentially sensitive population consists of people who are under the influence of opiate or other drugs. Opiates act to decrease the cough response (Fuller et al., 1988), increasing the dose to the deep lung; similar studies were not located for other drugs. Preliminary animal data from Crouch et al. (2003) indicate that, for a given delivered dose, cocaine and amphetamines may also increase tissue sensitivity to capsaicinoids. Complicating the matter further, people under the influence of drugs are often harder to incapacitate, and so may receive multiple sprays of OC, resulting in a higher dose. Because this population appears to be particularly susceptible to deaths in custody, it would be useful to obtain more information about the interactions between capsaicinoids and alcohol, cannabis, cocaine, and amphetamines.

The threshold for pulmonary effects was extrapolated from a dose that did not induce SE 2 level effects in animals using an uncertainty factor approach, based on standard methods used in chemical risk assessment. A factor of 3 for animal to human extrapolation and a factor of 3 for human variability were selected, resulting in a composite uncertainty factor of 10. This factor is reasonable in light of the extrapolation from deposited dose, but is an estimate. In addition, the observed variability in the data means that the actual no effect threshold for SE 2 level effects is not known very precisely.

The threshold for effects from aspiration of liquid was based on a report of an effect level for pulmonary effects in aspiration events. No threshold was identified, so the threshold for SE 2 effect was extrapolated from the effect level using a factor of 10. No additional factor for human variability was used, because the starting point was a range, already reflecting some variability. However, this approach does not provide a very precise estimate of the threshold either. Separate thresholds were used for the child and adult, but the same dose estimate was used for both. This is likely an over-estimate of the child dose, because it does not account for a child's mouth being smaller than the adult mouth.

6.3.1.4 Skin Effects

A qualitative approach was used for effects on the skin, because irritation is an SE 1 effect, but not being tracked as an indicator response for effectiveness. In addition, extensive field experience indicates that concentrations of capsaicinoids used

in these sprays are likely to greatly exceed the thresholds for irritation. Prolonged exposure to ethanol can also cause skin irritation, but the potency is much lower than that of capsaicinoids, and prolonged exposure is unlikely, since decontamination procedures include washing of the skin. The primary uncertainties for the skin endpoint are how to account for human variability (e.g., genetic polymorphisms, age-based differences in skin thickness, and hypersensitivity) as well as factors that modify exposure (particularly the effect of humidity). Rare polymorphisms may result in much more severe skin reactions (severe edema, blistering) under conditions of normal use, but field use experience indicates that such hypersensitivity reactions are very rare. On the other hand, some data suggest that some polymorphisms or ethnicity may impart decreased skin pain responses, which may account for decreased response in some Asian populations (L. Pershing, personal communication, July 28, 2004). Skin abrasions would increase the sensitivity to skin effects of both capsaicinoids and ethanol, but no quantitative estimate of the magnitude of this impact was available.

6.3.1.5 Other Effects

Several uncertainties were identified for systemic effects of capsaicinoids. Increased blood pressure that is likely to be secondary to pain was considered to be of concern for certain populations, but was not evaluated due to the absence of sufficient quantitative data. It would be useful to obtain additional data on blood pressure immediately after confrontations. While some studies did measure blood pressure following field use, the delay from the initial exposure was long enough that significant transient effects could have been missed. Significant data gaps also exist regarding the potential for increased intraocular pressure and (RADS), since only effect identification was possible for these endpoints, based on extrapolation from other sensory irritants; no data were located on the potential for these effects following exposure to capsaicinoids. Reports of field-use exposures that required medical treatment suggest that severe effects secondary to these effects are uncommon or have gone unreported. However, it would be useful for people responsible for the triage and medical treatment of people exposed to capsaicinoids to be aware of these potential complications and the potential effects of solvents in the formulation, so that the treatment of individuals who may be at increased risk from medical complications can be appropriately monitored.

Another primary data gap was the absence of data via the oral, inhalation, or dermal routes regarding neurodevelopmental toxicity, and developmental delays in reproductive function. These endpoints are of concern in light of the findings in injection studies of nerve degeneration and impaired postnatal growth, as well as impaired development of reproductive function. A neurodevelopmental toxicity study via an environmentally relevant route would be useful to evaluate this potential. Alternatively, a functional observational battery (FOB) and detailed evaluation of histopathology of the nervous system could be included in a standard toxicity study designed to evaluate the systemic effects of repeated exposure by a relevant route.

Data gaps were noted in a number of other systemic endpoints, as described in Section 6.1. While it would be of interest to address these data gaps, the available data indicate that none would likely impact the key conclusions of this HERC.

Ethanol is a common solvent for OC sprays, and a 50% ethanol:water mixture is the solvent for the PAVA sprays used for this “illustrative” assessment. No data gaps

affecting the assessment for ethanol were identified. This HERC did not evaluate the potential health effects of the solvent or aerosol components of OC sprays, but did note that solvents typically used can cause eye and respiratory effects following exposure during normal use scenarios, and possible neurological effects at high doses. A summary of the possible effects of solvents is in Appendix B, but no dose-response assessment was conducted for any of these effects. Further investigation of these endpoints would be useful. Alternatively, standardization of OC sprays and specification of which solvents are safe would be useful.

A final data gap noted in the effects identification is tachyphylaxis, the reduced response following repeated stimulation by capsaicinoids. Tachyphylaxis is well described in the pharmacological literature on skin responses. This effect did not occur in studies of the effect of capsaicin on respiratory effects, but exposures were short and the total dose was low. Some degree of decreased effectiveness with repeated exposure was reported by officers using OC delivering a small aerosol droplet size, but it was unclear whether this reflected tachyphylaxis or whether increased familiarity with the spray resulted in an increased willingness to "fight through" the effects of the spray. Conversely, decreased effectiveness of PAVA delivered as a large-droplet-size aerosol was reported in Thailand, although it was not clear if this was due genetic differences or the high capsaicinoid intake in that culture.

6.3.2 Exposure Uncertainties and Data Gaps

In general there is little or no information on the characteristics of the aerosols produced by the various devices. Data on factors such as, the spray angle, nozzle velocity, and droplet size distribution were not identified for any commercially-available product. Without data on these factors it is impossible to determine the true frequency of the production of respirable aerosols in the spray. In addition, this limitation prevents the accurate modeling of the aerodynamic properties of the two products (i.e., the distance the sprays can reach, spread of sprays with distance, and the velocity of the droplets at various distances).

Additional empirical studies on the behavior and transport of droplets formed by these devices would also be useful. Such studies could include placing air sampling devices on individuals (or mannequins) and directly measuring doses to the eye and the amount of respirable droplets in the target individual's breathing zone. The studies should also include an evaluation of the impact of factors such as wind, distance, and the ability of the user to aim the devices. Such data would allow the calibration of the exposure models developed for this project to specific aerosols and improve the quality of the exposure estimates.

Most manufacturers do not provide sufficient information on their products in their labels, user handbooks, or web sites to allow an independent assessment of effectiveness, safety use, hazards and risks. Data are required on the composition of OC, nature of propellant, solvents used, and droplet size distribution. Other information needed for a complete assessment is listed in Tables 12 and 13 of Section 5.

No data were identified on the actual amounts of spray used to control individuals. As a result, the estimates of dose in this analysis could under- or over-estimate actual exposures. One type of data that would address this need is weigh

in/weigh out data. This type of data requires that each device is weighed when purchased and reweighed after each use.

While limited field data on effectiveness were identified, insufficient information was available to tie the effectiveness to quantitative exposure data. A program of interviewing officers who use the devices and systemically tracking the conditions of use and associated effectiveness would be of great value.

A key finding of this report is the potential for indoor use of foggers to produce significant and ongoing exposures (lasting up to 20 min) to capsaicinoids for a single shot from a fogger. This finding should be confirmed by a monitoring study of air levels of capsaicinoids that occur as a result of fogger use.

6.3.3 Summary of Research Needs and Data Gaps

6.3.3.1 Research Needs

The following bullets summarize research needs related to developing a complete assessment as well as data gaps that do not relate to key research needs. While filling these latter data gaps may be of interest, it is highly unlikely that filling these data gaps would affect the results of the HERC.

- Comparative dose-response data for PAVA, capsaicin, and dihydrocapsaicin for key endpoints;
- Definition of effectiveness for small-droplet-size aerosols;
- Systematic statistically rigorous reporting system to measure effectiveness and adverse effects;
- Identification of a predictive dose metric for pressure injuries to the eye that applies to water droplets emitted from a variety of devices;
- Improved deposited dose estimates for the respiratory tract;
- Dose-response information for laryngospasm;
- Improved understanding of the relationship between the dose-response for bronchoconstriction in asthmatics and the dose-response for effectiveness in normal subjects and asthmatics;
- Information on the impact on effectiveness in individual under the influence of drug or alcohol;
- Effects of repeated exposure, particularly on the respiratory tract;
- Improved estimate of the threshold for pulmonary effects, based on reliable dose-response data;
- Development of a self-contained pulse oxymeter that could be used on restrained people and under conditions of fogger exposure to monitor for adverse bronchoconstriction.
- Dose-response information on neurodevelopmental effects;
- Quantitative information on tachyphylaxis (reduced response after repeated exposure);
- Quantitative information on the impact of temperature and humidity on both the dose-response of capsaicinoids, and on exposure from OC and PAVA devices;
- Additional studies on the behavior and transport of droplets formed by OC devices;

- Data on the actual amounts of spray used to incapacitate individuals and the specific products used;
- Information on the composition of specific products;
- A survey of effectiveness for the different types of devices, including reporting of the conditions of use, which will allow for the determination of the influence of these conditions;
- A monitoring study of the distribution and persistence of aerosols following the use of foggers;
- Information on the potential for capsaicinoids to cause increased intraocular pressure and increased blood pressure in humans. This data could be obtained in controlled exposure studies. If such studies are conducted, it would also be of interest to collect data on hematology, clinical chemistry, and neuropsychological endpoints.
- Information on thresholds for ocular effects of solvents
- Estimate of an SE 2 effect threshold for pulmonary effects of liquid aspiration
- Toxicology studies: *In vitro* skin penetration; repeated inhalation exposure (up to subchronic) studies; developmental toxicology studies in two species (including monitoring of neurobehavioral and neuropathological endpoints); a two-generation reproduction study.

6.4 COMPARATIVE RISKS

All NLW systems are associated with intended effect(s) and unintended effects. If the severity and probability of occurrence for each of the intended effects are favorable in comparison to those of the unintended effects, then the NLW system will likely have utility as well as greater public and policy acceptance. A comparison of the relative probability of the intended and unintended effects from the use of the chosen NLW system/payload to other NLW systems/payloads, or even to the use of lethal force, or not employing any alternatives, can assist in the determination of the value of a weapon system.

This report highlights the potential for intended and unintended effects resulting from the use of OC and PAVA. An additional aspect of the characterization of risks associated with these riot control agents is comparison of the risk of adverse effects from the use of these agents with the risk of adverse effects from other non-lethal or less-than-lethal technologies, and the effect on these risks of adopting the agent as part of the use-of-force continuum. Several studies have reported the impact of the introduction of OC or PAVA on injury rates for police officers and suspects from conflict situations. These reports indicate a significant reduction of injuries to both groups of individuals.

In an extensive side-by-side comparison of riot control agents, Recer et al. (2002) compared the health effects of OC, CS, and 2-chloroacetophenone (CN) as part of an evaluation for the New York State Department of Health. Based on a comparison of the acute toxic potential of these agents, they concluded that the risk of serious effects is low for all agents, but that the potential for chemical burns and serious lung effects is higher for CS and CN than for OC. The potential for skin sensitization and blistering was also higher for CS and CN. These conclusions were supported by sales-

normalized data on exposure incidents reported to poison control centers (admittedly an incomplete reporting source). The authors also stated that OC is harder to resist. Based on these results, the Department of Health developed a rule in 1997 that specified OC as the only active ingredient to be used for self-defense sprays for sale and use in the state. The rule also specified a maximum capsaicinoid content of 0.7%, and specified additional conditions regarding the packaging and labeling of such devices. Supporting this conclusion, Debarre et al. (1999) found that, using similar aerosols, inhalation of 5% CS caused more severe respiratory effects than inhalation of 7% OC. Busker and van Helden (1998) noted that CS and CN are direct-acting irritants, and people with a high pain threshold are more resistant to their effects, while OC causes involuntary eye closure and shortness of breath. In addition, OC acts essentially immediately, while CS and CN require an interval of 20-30 s for incapacitation.

A recent comparison of CS and PAVA[31] has also been published by the U.K. Home Office Scientific Development Branch (2004). The report summarizes the relevant effects and operational data for each agent separately. A conclusion regarding the comparative effectiveness and risks of these two riot control agents was purposely not included in the report. The absence of a general comparison reflects that each agent has its own advantages and disadvantages, and selection of the most appropriate agent to deploy could be best made locally based on the operational needs. The report does note that statements from expert medical committees "support the use of both PAVA and CS spray in their current formulations by UK police providing the guidelines for use are adhered to (Home Office Scientific Development Branch, 2004, p. iii)." Furthermore, most officers interviewed commented that they each material could provide an operational advantage depending on the situation with which they were faced. Based on compilation of comments from officers (many having experience using both agents) a key advantage of CS was the decreased need for accuracy. This presumably reflects the comment that "as long as the CS spray hits a person there is normally some effect" (Home Office Scientific Development Branch, 2004, p. 4). A key advantage of PAVA was the decreased probability of cross-contamination. This reflects the comment that cases requiring decontamination of equipment were not identified by the authors.

In a review of OC use in Austria, Holzer (1998) reported "immunity" in 2% of the people sprayed, compared with approximately 20% of the people sprayed with CS. In the 4-year period evaluated, Holzer reported an increase in weapon use by 15% (due to a 300% increase in the use of non-lethal weapons), together with a decrease of firearm use by about 45%. Personal injuries were reduced by about 60% and property damage by about 50%. Injuries to officers decreased by about 75% in one year, and by about 25% in other years. Holzer recommended use of a stream device, due to the greater range, lower risk to bystanders and users, and lower risk of airway inflammation. He noted, however, the greater difficulty of striking the face with the stream, compared to a cone spray, presumably due to the difficulty of striking a moving target with a narrow stream.

[31] The report did not state whether the chemicals were evaluated generically, or as delivered by specific devices, although some statements suggested that specific devices were being considered.

A review of OC for the New Zealand Police National Headquarters (Crane, 1997) noted user data from a variety of law enforcement agencies that the use of OC has resulted in a decrease in the use of force and that resultant injuries to both police and the public have been reduced. Crane also noted that the data she reviewed did not include detailed records made in an identical manner before and after the introduction of the OC spray. An NIJ-funded study conducted in North Carolina found a decline in injuries to police officers and suspects, as well as in complaints of the use of excessive force, after the introduction of OC spray (Ashcroft et al., 2003). The authors noted that the procedures for identifying injuries differed across agencies, however, limiting the results of the study.

Since any use of OC involves some risk of pain, if not more adverse effects, several researchers have addressed treatment and decontamination approaches. Some users noted that after they reach the police station, they have the subject swish the face in a bucket of water with eyes open to remove the capsaicinoid from the eyes. Crane (1997) recommended that officers carry an aerosol bronchodilator and spacing device, and be trained in the recognition of breathing difficulties and administration of such treatment, to avoid deleterious effects from bronchospasm. Antidotes that can be applied to the eye and relieve the pain have also been investigated, since the pain may continue for half an hour after compliance is achieved.

Training plays a very important role in the effective use of OC and PAVA. As noted in Section 3.2, OC typically does not cause 100% incapacitation and compliance in field use; officers need to be aware of the limitations of the incapacitant, or they run the risk of injury due to incomplete compliance. (This also applies to PAVA, although reported incapacitation is much higher, expressed as a percentage of the times the spray hits the face.) Training is also necessary in appropriate targeting of the devices, particularly for the streams. While police forces undergo this training, consumers generally are not informed of the need for such training or the limitations of the device. Training can also be useful in avoiding over-reliance on the incapacitant. A user abroad noted that training was necessary to maintain the use-of-force continuum, so that officers did not turn too readily to the incapacitant before trying to reason with the individual. Finally, obtaining compliance without any use of force is optimal for risk reduction and professional judgment is required regarding appropriate uses. One of the more controversial uses of OC has been its application with a cotton swab to the corners of the eyes of nonviolent protestors.

6.5 RISK CHARACTERIZATION SUMMARY

Our analyses suggest that, despite significant data gaps in exposure and toxicity, devices that spray liquids containing OC and PAVA are generally effective devices, achieving a significant degree of compliance that appear to have a limited potential for moderate to severe unintended effects. This conclusion is consistent with several other recent evaluations of OC or PAVA. However, there are significant and important uncertainties in the effects assessment, particularly regarding dose-response for respiratory effects of small-droplet-size aerosols and the estimates of inhalation exposure and physical impact of droplets on the eye.

The potential for occurrence of the various effects evaluated in this HERC can be summarized as follows:

- Eye effectiveness – expected for both the cone and stream, as long as the spray reaches the eyes; not effective for the fogger.
- Pressure injury to the eye – not a concern for the fogger; streams or cone sprays that produce droplets (greater than 26 m/s) may pose a significant risk of severe eye damage.
- Respiratory effectiveness – expected within 1 minute or less for the fogger.
- Bronchoconstriction in sensitive asthmatics - not expected for the stream or cone sprays; may occur within 1 minute or less for both fogger scenarios, but the fraction of the population where this effect will occur is not known, due to considerable variability among asthmatics.
- Bronchoconstriction in healthy individuals – not expected for the cone spray or stream; there may be some risk for bronchoconstriction in healthy individuals from foggers, but the dose that causes bronchoconstriction in healthy individuals is not well defined.
- Pulmonary effects – not expected for the cone spray or stream; there may be a risk of pulmonary effects for fogger and this risk will increase with foggers that have low levels of solids, but the data are not sufficient to translate this potential into a probability of an effect.
- Aspiration of liquid – not a concern for the fogger; not a risk based on aspiration of inert liquid for the stream or cone spray device investigated in this study. However, the lack of data on the actual amount used and the frequency of use at a distance of less than a meter prevent the elimination of concern for this effect.
- The risk of flammability depends on the solvent mixture. The available data suggest that the 50% ethanol:50% water mixture used in the hypothetical three devices assessed in this report have the potential for being ignited under certain circumstances.

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Human Effectiveness and Risk Characterization of Oleoresin Capsicum (OC) and Pelargonic Acid Vanillylamide (PAVA or Nonivamide) Hand-held Devices

Part II – Appendices

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16 May 2007

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Appendix A - NLW Framework Overview

The following is extracted from Risk Characterization of Non-Lethal Weapons: Report of Expert Workshop and Proposed Conceptual Framework (TERA, 2001).

Non-Lethal Weapons (NLWs) are becoming increasingly important assets in nontraditional military operations, such as peacekeeping missions or humanitarian aid operations, where the use of lethal force may not be a desired first response for force protection. NLWs are weapons that "are explicitly designed and primarily employed so as to incapacitate personnel or materiel, while minimizing fatalities, permanent injury to personnel, and undesired damage to property and the environment" (DoD, 1996, p. 2). Various types of weapons are part of the Department of Defense (DoD) non-lethal weapons program, employing riot control agents, electromagnetic, mechanical, or acoustic technologies. DoD Directive 3000.3 calls for these weapons to "achieve an appropriate balance between the competing goals of having a low probability of causing death, permanent injury, and collateral materiel damage, and a high probability of having the desired anti-personnel or anti-materiel effects" (DoD, 1996, p. 5).

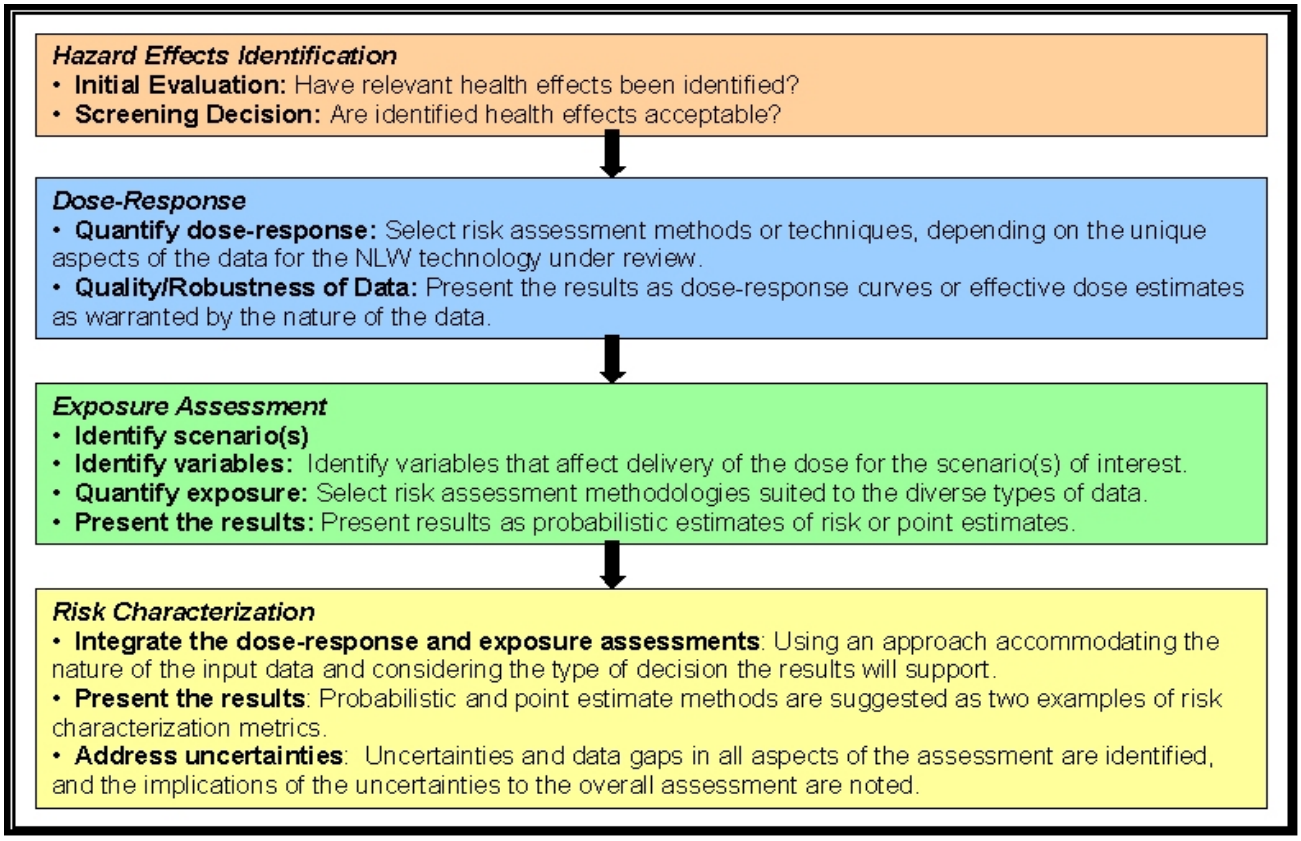
In an effort to achieve this balance, Toxicology Excellence for Risk Assessment (TERA) was asked to organize a workshop of leading risk assessment experts, who were joined by Subject Matter Experts (SMEs) from the DoD and its contractors, to develop a framework for characterizing the risks from military use of NLWs. The results of risk characterization are to provide decision-makers with the probability of intended target response effects and unintended effects so that the risk could be weighed against the effectiveness and benefits of using NLWs.

The workshop participants met in May 2001 and explored ideas to identify, evaluate, and quantify risks from NLWs for users, targets, and bystanders; ultimately, they developed a proposed conceptual framework (TERA, 2001). The independent external review panel (IERP) recommended that the four steps of the National Academy of Sciences risk assessment approach (i.e., hazard identification, dose-response assessment, exposure assessment, and risk characterization) serve as a foundation for the framework.

This conceptual framework is described in Table A-1 and focuses on the physiological effects and immediate behavioral consequences of those effects caused by the weapons. It allows risk assessment experts to integrate information on intended target effects and risks of unintended effects. Its purpose is to facilitate the organization of available data, to communicate risks and benefits to different levels of decision-makers, and to identify research needs. The Human Effectiveness and Risk Characterization (HERC) that emerges from the framework should integrate information from the dose-response assessment and the exposure assessment to evaluate the level of risk for the population or individual and compare that to the target response effectiveness. Field commanders and mission planners could use the resulting information to make informed choices

regarding which NLWs would provide the most appropriate combination of target effectiveness and risk for the particular situation or mission.

Table A-1. Overview of the Conceptual Framework for Risk Characterization of Non-lethal Weapons (from TERA, 2001).



The IERP convened by TERA concluded that application of risk analysis tools routinely used in human health risk assessment and elsewhere seems to offer great promise for analysis of effectiveness and risk associated with NLWs, both for existing NLWs and those under development. Risk characterization proceeds in tandem with better understanding of the relationships between the biophysical forces delivered by the weapons, the range of behavioral responses to these forces, and the biophysical mechanisms of potential injury. This proposed effectiveness and risk characterization framework could enhance risk communication with stakeholders who influence the sociopolitical environments in which these NLWs might be developed and deployed.

The framework walks the analyst and decision-maker through a series of steps, which identify the types of human effects anticipated from a particular weapon and the relationship between amount of "dose" (or force of the weapon) and the resulting response. For a given scenario or set of circumstances, the effect of exposure conditions on the amount of force or "dose" received by the exposed persons(s) is estimated. This information on the dose-response relationship and the dose received by exposed persons are then combined to describe the potential risk of adverse effects to potentially three groups: the

person(s) who is (are) the target, the operator or user of the weapon, and bystanders who are not intended targets. The effectiveness and risk characterization description includes the probability of inducing a specific type of physiological response or group of responses, injury or death given certain circumstances. If the data are more limited, the results may provide an indication of the margin of safety between the amount of dose resulting from an exposure likely to result from a given situation and the dose that would induce intended and unintended effects.

The conceptual framework for risk characterization of non-lethal weapons framework is based on a process framework developed for the evaluation of chemical substances (NAS, 1983) and uses the term "dose" in a generic sense. Dose in the context of non-lethal weapons effectiveness and risk characterization refers to a quantitative measure of the substances or forces released by a non-lethal weapon that contact/reach an individual as a result of the use of a non-lethal weapon and are available to induce a physiological response. Similarly, "dose-response" refers to the relationship between that quantitative measure of the substances or forces that reach the individual and the observed response. These definitions apply generically regardless of the appropriate units of the "dose," although more precise terms are used when possible for individual endpoints. For example, certain non-lethal weapons produce their effects by conveying chemical substances to individuals, with the chemical substances producing the observed effects. Other non-lethal weapons cause effects by conveying kinetic energy (blunt trauma), acoustic energy (sound), or electromagnetic force (light, radiant heat, or electricity) to individuals. The appropriate measure of "dose" depends on how the weapon produces its effects, both in terms of the type of exposure and the mechanism for causing the effects. For example, for chemicals, the "dose" may be expressed as the concentration in air or applied to the skin, the concentration in air weighted by some measure of duration factor, the amount in mg, the amount ingested scaled by body weight (e.g., mg/kg). For other types of non-lethal weapons forces released, the "dose" may be expressed using units such as measures of heat, pressure, or intensity of light. The term "dose" also has specific definitions in toxicological contexts, although some aspects of the definitions may vary. For example, one classic text defined "dose" as and is defined as:

> "The amount of material to which an organism (or test system) is exposed, usually by a specific route. It is referred to as the acute dose when it results from a single exposure and as the cumulative dose when totaled over a series of repeated exposures. Dose can also be qualified as: (a) the *exposure dose*, which is the total amount of material to which the organism is exposed (or incorporated into the test system), as (b) the *absorbed dose*, which is the amount of material gaining access to the interior of the organism by absorption through the route of exposure into the systemic system; absorbed dose thus usually shows a quantitatively closer relationship to systemic toxicity than does exposure dose, and as (c) target dose which is the amount of material received at the particular organ or tissue exhibiting a specific toxic or pharmacological effect; and is ideally expressed as the mechanistically causative molecule (parent chemical or reactive metabolite)" (Ballantyne et al., 1999, p.9).

Certain non-lethal weapons produce their effects by conveying substances to individuals and having the substances produce toxicological effects. Other non-lethal weapons cause effects by conveying kinetic energy (blunt trauma), acoustic energy (sound), or electromagnetic force (light, radiant heat, or electricity) to individuals. In this report, the term "dose" is applied to both the mass of chemical and to the amount of energy or amount of force that reach the exposed individual as a result of the use of a non-lethal weapon. The units of dose will be determined by the mechanism by which the non-lethal weapon produces the effect and the units used in the "dose"-response portion of the assessment. Under this expanded definition, "dose" is defined as a quantitative measure of the substances or forces released by a non-lethal weapon that reach an individual as a result of the use of a non-lethal weapon.

As for each step of the framework, Figure A-1 illustrates that if there are not sufficient data to identify the weapon's effects, more research is recommended. Similarly, additional research may be needed if there is insufficient data for the dose-response assessment or exposure assessment.

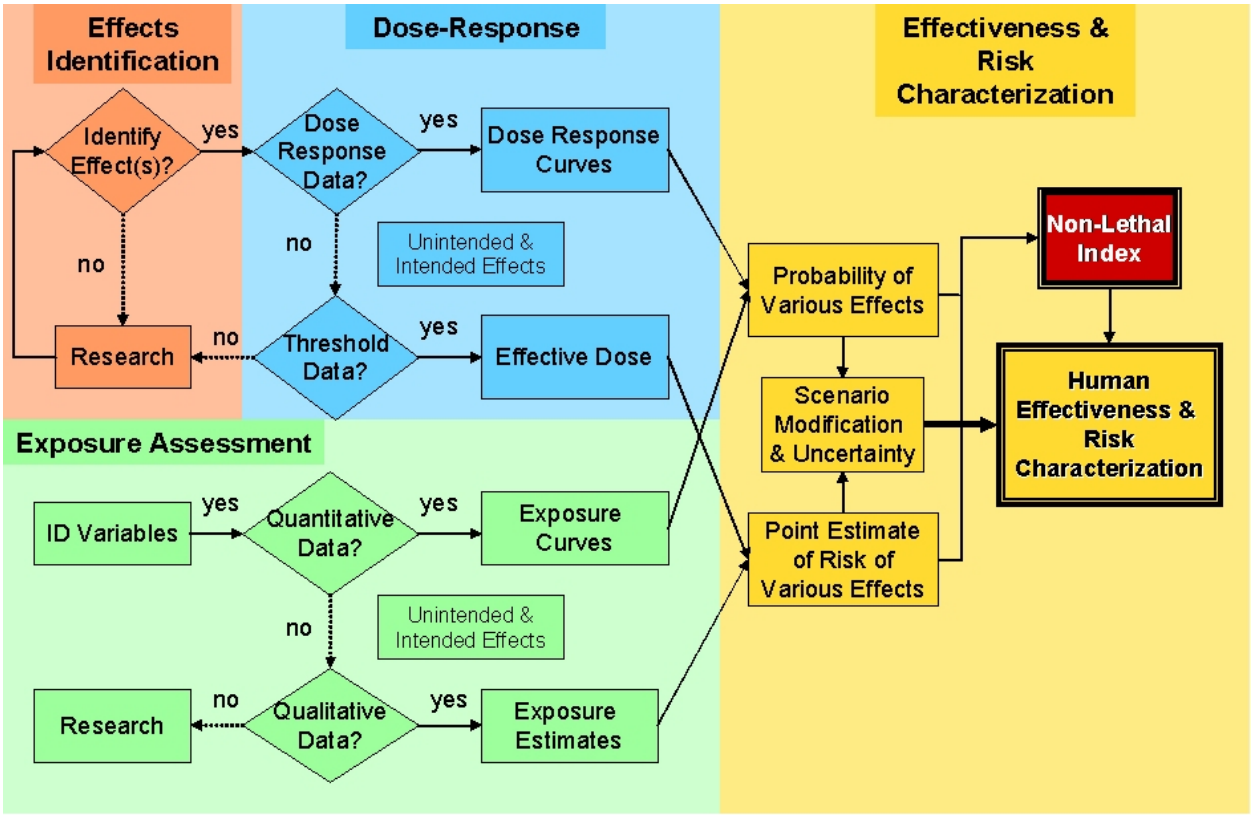


Figure A-1. Conceptual Framework for Effectiveness and Risk Characterization (Revised 2003).

This flow chart outlines the steps needed to characterize effectiveness and risk from use of non-lethal weapons. The effectiveness and risk characterization description is the end result of the process reflecting hazard effect identification and dose-response data incorporated in combination with the exposure

assessment. If there are not sufficient data to identify the weapon's effects, more research is recommended. Similarly, additional research may be needed if there is insufficient data for the dose-response assessment or exposure assessment. These results in the risk characterization column (either probabilities or point estimate ratios) reflect the type of decision needed as well as data available from the dose-response and exposure assessments.

Definition of Terms

A number of terms are used in the framework document and are defined as follows:

Users or Operators: in this context, the user or operator refers to the person(s) deploying the non-lethal weapon.

Targets: the target population refers to the individuals against whom the weapon system is being employed.

Bystanders: bystanders refer to all other individuals that may be affected by the use of the non-lethal weapon, excluding the target (collateral individuals).

Human effects: as applied to NLWs, may include any of the following: physiological/health effects to the weapon operator, human targets, and bystanders near the target, and effectiveness of the weapon against human targets.

Intended effects: the intended effect of the non-lethal weapon on the target to accomplish specific mission tasks and subtasks. While intended effects may be behavioral responses, generally only the physiological effect (e.g., pain, heat, or eye irritation) is directly measurable. Throughout this report the term "intended effect" is used to indicate the measurable physiological effect that serves as a surrogate for the intended behavioral response.

Unintended effects: effects that produce injury or death to the targeted individuals against which whom the non-lethal weapon is employed. Injury may refer to serious irreversible physiological effects that impact on living capabilities, such as blindness, hearing loss, or paralysis. For bystanders or users, unintended effects may be considered any adverse unwanted human effect, including those that would be intended and desired for the target.

Dose: a quantitative measure of the substances or forces released by a non-lethal weapon that reach an individual and are available to induce physiological responses as a result of the use of a non-lethal weapon. Quantity of an active agent (substance or radiation) taken in or absorbed at any one time (Cognitive Science Laboratory at Princeton University, n.d.)

Dose Response: the quantitative relationship between the delivered dose from a non-lethal weapon and the magnitude of an effect in an individual.

Exposure: the interaction of an individual and a non-lethal weapon during or following the use of the weapon.

Severity/Effectiveness Level 1 (SE 1): self-limited injury that will completely resolve by itself.

Severity/Effectiveness Level 2 (SE 2): more persistent, serious or extensive effects, ideally receiving medical evaluation/treatment, but still capable of healing without special intervention.

Severity/Effectiveness Level 3 (SE 3): potentially life-threatening effect or risk of significant residual disability. Needs hospitalization and/or specialist care.

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Appendix B - Solvents and Propellants

A significant limitation to this HERC for OC is that, unlike the devices analyzed under previous HERCs, OC and PAVA sprays are a diverse set of more than 300 commercially-available products, varying in the identity and percent of the solvents and propellants used. The tables below list a variety of common solvents and propellants used in many of the hand-held OC sprays (Conrad, 2004), and the potential health effects caused by exposure to these chemicals. These tables provide an overview of the potential health effects, based on secondary literature sources and toxicity summaries such as the Hazardous Substances Data Bank (HSDB), the International Programme on Chemical Safety (IPCS), the Agency for Toxic Substances and Disease Registry (ATSDR), and the Registry of Toxic Effects of Chemical Substances (RTECS).

While the information in these tables are useful for identifying potential effects of interest as part of Effects Identification, they cannot be used to predict the probability of these effects occurring following exposure to an OC device. No dose-response information is presented below, and such information coupled with exposure estimates is required to determine whether effects may occur. For solvents in general, many of the acute systemic effects (e.g., neurological symptoms) are only seen when the exposure is at high concentrations, which may be above those associated with the use of some OC devices. However, as noted below, systemic effects of solvents following use of self-defense sprays have been reported at least in some cases. Fast-acting direct contact effects (e.g., eye and skin irritation) are more likely to occur with typical OC device use. Some effects noted here are likely only after repeated chronic exposures, and may not be of significant concern for single or infrequent exposure from an OC device. These principles were described in the HERC using ethanol in the context of the PAVA spray as an illustrative example.

Chemical	CASRN	Potential Health Effects	
		Acute Exposure	Repeated/Chronic Exposure
Solvents			
sec-Butanol	78-92-2	Irritation[1] Neurological effects[2] Gastrointestinal irritation[3]	Dermatitis
Dichloromethane (Methylene Chloride)	75-09-2	Irritation (including temporary corneal damage) Neurological effects (resulting from CNS depression as well as systemic carbon monoxide poisoning, including memory loss, impaired speech and balance, delirium, blurred vision) Gastrointestinal irritation	Dermatitis Liver effects Carcinogenic effects
Dipropylene Glycol	34590-94-8	Irritation	Dermatitis

Methyl Ether		Neurological effects	Kidney effects Liver effects
Isopropyl Alcohol	67-63-0	Irritation Neurological effects	Dermatitis Liver effects Kidney effects
d-Limonene	5989-27-5	Irritation Skin sensitization Gastrointestinal irritation	Dermatitis
Propylene Glycol	57-55-6	Irritation Gastrointestinal irritation Neurological effects (seizures) Metabolic effects (hypoglycemia and lactic acidosis)	Dermatitis Liver effects Kidney effects
Tetrachloroethylene	127-18-4	Irritation Neurological effects	Dermatitis Liver effects Kidney effects
Trichloroethylene	79-01-6	Irritation (including temporary corneal damage) Neurological effects (including optic neuritis and blindness, hearing loss) Irregular heartbeat	Dermatitis Neurological effects (including neuropathy, nerve palsies, dementia, oculomotor paralysis, hearing loss, loss of feeling in extremities, loss of memory) Liver effects Kidney effects Carcinogenic effects
Propellants			
n-Butane	106-97-8	Neurological effects Cardiac sensitization	None
Carbon Dioxide	124-38-9	Hypoxia (secondary to oxygen deprivation)	None
Nitrogen	7727-37-9	Hypoxia (secondary to oxygen deprivation)	None
Propane	74-98-6	Neurological effects Cardiac sensitization	None
1,1,1,2-Tetrafluoroethane	811-97-2	Neurological effects Cardiac sensitization	Liver effects

1. Unless specified otherwise “Irritation” refers to potential eye, skin, and respiratory tract irritation. Irritant potency is not listed here.
2. Neurological effects refer to the spectrum of symptoms resulting from central nervous system depression. These effects increase in severity with exposure with a typical presentation of signs and symptoms beginning with headache, dizziness, nausea, followed by ataxia, narcosis, coma and death. Other specific effects of an agent are noted in parenthesis.
3. Typical signs of gastric irritation would include nausea, vomiting, and diarrhea.

It is clearly important that the solvents and propellants used in hand-held self-defense sprays may constitute a major percent of the total composition of the spray. In the absence of a full dose-response analysis, documented accounts of

both local and systemic adverse health effects resulting from overexposure to solvents in self-defense sprays provide insights into the types of effects that may occur under field use situations. Some substances that have been used as solvents in riot control agent formulations are known to produce local toxicity. These effects include moderate acute eye injury and increased IOT (intraocular trauma) from dichloromethane (Ballantyne et al., 1976), and irritant dermatitis from methyl isobutyl ketone (MIBK) (Gray, 2000). It has been experimentally demonstrated that with an aerosol generator of CS dissolved in dichloromethane, both materials contribute to the ocular inflammation resulting from contamination of the eye (Ballantyne, 1979). Local cutaneous toxicity from the use of CS dissolved in methyl isobutyl ketone (MIBK) was reported for individuals exposed to this formulation in police personal incapacitant sprays (Euripidou et al., 2004). The skin lesions described were erythematous dermatitis and blisters that persisted for longer periods than anticipated from exposure to CS alone. This indicates that the MIBK may have enhanced local cutaneous effects. Softening and fragmentation of contact lens may occur due the solubilizing effect of solvents (Ballantyne, 2005). Also, some solvents, such as trichlorethylene, may lead to hardening of contact lenses and resultant physical damage (Holopainen et al., 2003). In addition to causing local ocular injury, dichloromethane may also result in systemic toxicity following inhalation, due to its hepatic metabolism to carbon monoxide (Horowitz, 1986; Rioux & Myers, 1988, 1989). A case of symptomatic carbon monoxide poisoning was described in a 39-year-old female after she was exposed to the solution from a personal defense spray containing CS in dichloromethane; the carboxyhemoglobin (COHb) level was 20.4%, and she was successfully treated with 100% normobaric oxygen (Duenas et al., 2000). These same authors also recorded cases of symptomatic CO poisoning in three young boys (aged 4, 5 and 9 years old) who were exposed to CS in dichloromethane accidentally released from a personal protective device; the respective COHb levels were 16, 12, and 19%, and the boys were successfully treated with 100% normobaric oxygen. The formulation of the solution in these devices was probably 0.8% CS in 49% dichloromethane.

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Appendix C - Overview of OC

This appendix was written by Dr. Eugene Olajos for use in this report.

Chemistry and Analysis

Oleoresin Capsicum (OC)

Oleoresin capsicum is an oily liquid resulting from the solvent extraction of dried, ripe fruit of chili peppers (*Capsicum annuum* or *Capsicum frutescenes*). Unlike other riot control agents [e.g., CS (2-chlorobenzylidene malononitrile), CN (1-chloroacetophenone), and CR (dibenz (b,f) 1:4 - oxazepine)], oleoresin capsicum (OC) is a complex mixture - an excess of a hundred different compounds have been identified in oleoresin capsicum. Oleoresin capsicum contains capsaicin and its structural analogs, alcohols, aldehydes, ketones, various acids and esters, oxidation and polymerization products, and carotenoid pigments. Oleoresin capsicum, being a natural product, is thermally labile – extraction processes must be designed to minimize thermal degradation.

Capsaicin

Among the vanillylamides, capsaicin (N-[(4-hydroxy-3-methoxyphenyl)-methyl-(E)-6-nonenamide) is the major pungent component of oleoresin capsicum. Capsaicin (CAS# 404-86-4) is the principal pungent component in many peppers and is particularly noted for its irritant properties. Capsaicin is available in natural or synthetic form. Capsaicin is a solid, which is sparingly soluble in water. The hydrolysis rate is slow, and it is stable in storage. The synthesis of capsaicin has been reported (Nelson, 1919; Jones & Pyman, 1925; and Spaith & Darling, 1930). A thin layer chromatography method for the identification of capsaicin in oleoresin capsicum-based formulations of tear gas aerosol sprays has been reported (Jane & Wheals, 1972). An HPLC procedure for the detection of capsaicin in self-defense spray formulations has been described by Krebs, et al. (1982).

Capsaicinoids

The pungent components of oleoresin capsicum, known as capsaicinoids, comprise at least six compounds to include capsaicin. Depending on the variety of chili pepper, OC may contain from 0.01 to 0.1 % capsaicinoids. Capsaicinoids identified in oleoresin capsicum include the following structural analogs to capsaicin: dihydrocapsaicin (8-methyl-N-vanillyl nonamide, CAS# 19408-84-5), nordihydrocapsaicin (7-methyl-N-vanillyl octamide, CAS# 28789-35-7), homocapsaicin (trans-9-methyl-N-vanillyl-7-decenamide, CAS RN 58493-48-4), homodihydrocapsaicin, (9-methyl-N-

vanillyl decamide, CAS# 279-06-5), and pelargonic acid vanillylamide (nonivamide). Fung, et al. (1982) have described a set of analytical procedures for the identification of capsaicinoids in "tear gas" sprays. Using GC-MS, Haas and co-workers (Haas et al., 1997) reported major differences in composition found in samples of OC sprays from various sources.

Nonivamide ("synthetic capsaicin")

Nonivamide (pelargonic acid vanillylamide) is a capsaicin analog commonly referred to as "synthetic capsaicin." Constant and Cordell (1996) successfully identified nonivamide as a minor (~ ¼ %) capsaicinoid in the oleoresin capsicum from *Capsicum annuum*.

Pharmacokinetics/Pharmacodynamics

Uptake and Distribution of Capsaicin/Capsaicinoids

Saria et al. (1982) studied the distribution of capsaicin in rodent tissues following systemic administration. High levels of capsaicin were detected following intravenous dosing with central nervous system tissues exhibiting high levels of capsaicin. Distribution studies after subcutaneous (s.c.) dosing of capsaicin revealed slow diffusion from the site of application. Studies by Kim and Park (1981) indicated that capsaicin and structural analogs were poorly absorbed from the GI tract, which led Kawada et al. (1984) to further study the gastrointestinal uptake of capsaicin/capsaicinoids. Findings indicated a rapid uptake of capsaicin and dihydrocapsaicin from the small intestine and stomach. Regional uptake of capsaicin/capsaicinoids was also investigated, and the results indicated regional differences in the absorption of capsaicin from the GI-tract. The results by Kawada et al. (1984) are in concordance with *in vitro* results reported by Monsereenusorn (1980). The absorption characteristics of capsaicin and capsaicinoids via a critical uptake route, such as inhalation, have not been elucidated.

Metabolism and Fate of Capsaicin/Capsaicinoids

The bioconversion and metabolic fate of capsaicin and capsaicinoids are reasonably well understood and characterized. Capsaicin and capsaicinoids undergo Phase I metabolic conversion involving both oxidative and non-oxidative pathways. The liver is the site of the highest enzymatic activity followed by extrahepatic tissues (e.g., kidney, lung, and small intestine). Lee and Kumar (1980) initially studied the metabolic processes involved in the bioconversion of capsaicin and its analogs. They demonstrated the conversion to catechol metabolites via hydroxylation on the vanillyl ring moiety - findings later confirmed by Miller et al. (1983). Kawada and Iwai (1985) studied the metabolic conversion of dihydrocapsaicin, an analog of capsaicin. Dihydrocapsaicin was metabolized to metabolic products that were excreted in the urine mostly as glucuronides.

The metabolic conversion of capsaicin by the mixed function oxidase system to an electrophilic epoxide is an example of bioconversion to a reactive metabolite. Other pathways leading to the formation of highly reactive intermediates involve the formation of a phenoxy radical as well as the formation of a quinone type product (Surh & Lee, 1995). In addition to the above oxidative pathways, studies by Wehmeyer et al. (1990) have demonstrated that the alkyl side chain of capsaicin is also susceptible to enzymatic oxidation. Surh et al. (1995a) have provided evidence that capsaicinoids can undergo aliphatic hydroxylation (i.e., ω-hydroxylation). Via this pathway, capsaicin is metabolized to ω-hydroxycapsaicin – other analogs of capsaicin (i.e., nonivamide and dihydrocapsaicin) also undergo aliphatic hydroxylation. Surh et al. (1995a) postulated that aliphatic hydroxylation of capsaicinoids represents a detoxification pathway. Non-oxidative metabolic processes are also involved in the bioconversion of capsaicin (Kawada et al., 1984; Kawada & Iwai, 1985; Oi et al., 1992).

Biochemistry, Mechanisms, and Biological Interactions of Capsaicin/Capsaicinoids

No single mechanism of action can account entirely for the varied physiological and toxicological effects of capsaicin and capsaicinoids. A multiplicity of mechanisms and modes-of-action are responsible for the biological actions of these chemicals - including toxic/adverse effects. Although much of the following discussion focuses on adverse effects whose etiology stems from the interaction of reactive metabolites of riot-control agents with critical molecular targets, mechanisms of action may also involve less-highly reactive metabolites.

When discussing the biological actions of reactive intermediates, one should note that different degrees of reactivity exist among these toxic intermediates, ultimately influencing the degree of toxicity associated with a particular chemical. Thus, extremely reactive metabolites are likely to interact with many cellular targets, in close proximity of their formation. Whereas, less reactive intermediates may travel to distant sites within the cell and react with additional cellular targets (Nelson & Pearson, 1990). Adverse effects that may result from such toxic metabolites include mutagenesis, carcinogenesis, immunotoxicity, perturbations involving bioenergetic pathways, oxidation of macromolecules (i.e., DNA, proteins and lipids), alteration of detoxication processes/capabilities, cytotoxicity, and the activation of signaling pathways involved in pathologic processes and carcinogenesis. The mechanisms by which some of these toxic metabolites [e.g., phenoxy radicals, quinones, $\bullet CH_3$, and ROS (e.g., superoxide, hydrogen peroxide, hydroxyl radical)] can produce adverse effects may be somewhat straightforward or rather complex as in the case of toxic intermediates such as quinones.

Studies on the mechanisms/modes-of-action of capsaicin and its analogs have been the subject of many review papers and numerous research publications (Lembeck, 1983; Marsh et al., 1987; Wood et al., 1988; Bevan & Szolcsanyi, 1990; and Winter et al., 1990). One of the initial issues to be addressed was whether a

single mechanism of neurotoxicity can account for the capsaicin-induced degeneration. The widely accepted view is that the specific action of capsaicin on a subpopulation of afferent neurons involves the activation of a specific receptor ("the vanilloid" receptor) - refer to Szallasi and Blumberg (1990a,b;1992) and Szallasi et al. (1991). Structure-activity studies have demonstrated a requirement for both the vanilloid ring and acyl chain moieties for pharmacologic activity (Szallasi & Blumberg, 1999; Caterina & Julius, 2001). The capsaicin-sensitive "vanilloid" receptor has been characterized (Caterina et al., 1997; Hayes et al., 2000); moreover, a number of vanilloid receptor-like proteins have also been identified (Caterina et al., 1999; Schumacher et al., 2000; Delany et al., 2001). The activation of the "vanilloid" receptor leads to the opening of a particular type of receptor-operated cation channel, and the ionic mechanism has been elucidated (Marsh et al., 1987; Wood et al., 1988). Sodium and calcium ion influx leads to depolarization which triggers local release of neuropeptides, central protective reflexes as well as autonomic motor responses (Lundblad & Lundberg, 1984; Martling, 1987; and Stjarne, 1991). According to Jancso et al. (1984), the influx of Ca and Na leads to rapid cellular damage and eventual cell death by osmosis and calcium-dependent proteases.

Capsaicin-induced acute biological effects are due to the release of bioactive substances (substance P, calcitonin gene-related peptide (CGRP), and neurokinin A) from sensory nerves. These neuropeptides function in the communication of primary sensory neurons with other neural and non-neural cells (Salt & Hill, 1983). Release of various neuropeptides by capsaicin produces an altered neurophysiology of sensory neurons in the airway mucosa as well as neuro-mediated inflammation of the respiratory epithelium, of airway blood vessels, of glands, and smooth muscle. The above consequences lead to adverse effects such as bronchoconstriction, edema of the tracheobronchial mucosa, enhanced vascular permeability, enhanced mucous secretion, and neutrophil chemotaxis (Lundberg & Saria, 1982a,b; Hua et al., 1984; Lundberg et al., 1983a, b, 1984; Saria et al., 1985; Theodorsson-Norheim et al., 1985; Helme et al., 1987; Tominack & Spyker, 1987; Umeno et al., 1990; Blanc et al., 1991; and McDonald, 1992). The modes of action [e.g., the release of neuropeptides (e.g. substance P, neurokinin A), the involvement of CGRP, and the induction of ion fluxes in neurons] that underlie the biological actions of capsaicin have been elucidated (Nilsson et al., 1977; Jessell et al., 1978; Virus & Gebhart, 1979; Theriault et al., 1979; Miller et al., 1982; Lundberg et al., 1983a; Burks et al., 1985; Gamse and Saria, 1985; Hua et al., 1986; Bevan et al., 1987; Franco-Cereceda et al., 1987; Holzer, 1988). Responses such as bronchoconstriction, vasodilatation, and protein extravasation are mediated by substance P, which belongs to a group of biologically active peptides known as tachykinins.

Substance P is one of the more thoroughly studied of neurotransmitters (Stern, 1963; Leeman & Mroz, 1974; Lembeck & Gamse, 1982). The isolation and characterization of substance P was accomplished by Chang and Leeman (1970) and subsequently sequenced by Chang and colleagues (Chang et al., 1971). Substance P is postulated to have a neurotransmitter role in primary sensory neurons for central transmission of afferent information (Otsuka & Konishi, 1983)

and as a peripheral mediator of neurogenic inflammation and smooth muscle contraction (Lembeck & Holzer, 1979; Lembeck & Gamse, 1982). Capsaicin-induced effects, namely, bronchoconstriction, vasodilatation, and plasma extravasation are mimicked by substance P and/or inhibited by SP antagonists. Other physiological actions of capsaicin such as the chronotropic and inotropic effects on the heart are not mediated via substance P. As previously mentioned, capsaicin has been shown to release substance P.

Aside from the mode-of-action of capsaicin/capsaicinoids on sensory neurons, these substances manifest chemoprotective properties against the genotoxic effects of known carcinogens as well as exhibiting antioxidant activity. Capsaicin is one of several dietary phytochemicals with potential chemopreventive activity. The chemoprotective properties against mutagenesis and tumorigenesis by known carcinogens stems from the inhibitory action of capsaicin on microsomal monoxygenases involved in carcinogen activation. Capsaicin and its analog, dihydrocapsaicin, have been demonstrated to inactivate cytochrome P-450 HE1 and other isoforms (i.e., P450 1A2) of the cytochrome P-450 family (Surh et al., 1995b; Teel et al., 1997). Capsaicin has been shown to attenuate the mutagenicity of vinyl carbamate (VC) and N-nitrosodimethylamine (NDMA) as assessed in *Salmonella typhimurium* (Surh et al., 1995b). They noted that suppression of NDMA and VC-mediated mutagenicity by capsaicin correlated with their inhibition of P450-mediated metabolism, namely, N-demethylation and p-nitro-phenyl hydroxylation. The antimutagenicity of capsaicin was also studied by Azizan and Blevins (1995). Studies by Surh and co-workers (Surh et al., 1995b) revealed a substantial anti-carcinogenic effect of capsaicin, suggesting that capsaicin and capsaicinoids possess chemoprotective activity. They demonstrated that the pre-treatment of female ICR mice with capsaicin decreased the average number of vinyl carbamate-induced skin tumors by 62% at 22 weeks after promotion.

Further discussion on the mechanisms/modes of action is incomplete without a discussion centered on toxic metabolites (e.g., semiquinone and quinone derivatives, methyl radicals) of capsaicin and their biological interactions. In their review on the metabolism and toxicity of capsaicin, Surh and Lee (1995) have discussed the role of metabolic activation in capsaicin-induced toxicity, and the metabolic pathways involved in the bioconversion of capsaicin to reactive moieties. As indicated, metabolic activation of capsaicin to reactive intermediates via the hepatic cytochrome P-450 system includes the conversion to semiquinone and quinone derivatives. Quinones is a general term for a class of compounds that are endogenous biochemicals, are found in natural products, or are generated via metabolism of xenobiotics.

The quinone intermediate of capsaicin can be formed by either of the following metabolic pathways: (1) initial O-demethylation of the 3-methoxy group on the vanillyl ring with concomitant oxidation to the semiquinone or o-quinone derivatives or (2) O-demethylation of the phenoxy radical intermediate of capsaicin. Quinone derivatives of xenobiotics produce toxic effects *in vivo* including cytotoxicity, carcinogenicity, and immunotoxicity. Cellular damage can occur via alkylation of critical cellular proteins and/or DNA. In addition, it should be

noted that redox cycling of quinones generate adducts and the formation of reactive oxygen species (ROS). Production of reactive oxygen moieties can lead to severe oxidative stress in cells via the formation of oxidized cellular macromolecules. In general, these moieties can interact with nucleophilic sites of macromolecules such as proteins, DNA, and RNA – these interactions are thought to be critical in the etiology of capsaicin-induced cytotoxicity, mutagenicity, and carcinogenicity. The formation of a quinone-type intermediate is of considerable interest owing to the multiplicity of quinone-mediated effects that include alkylation of DNA and proteins, GSH depletion, reactive oxygen species (ROS) formation and ROS-related effects such as DNA oxidation and lipid peroxidation.

Quinones are activated metabolites of polycyclic aromatic hydrocarbons, and represent a class of reactive intermediates that produce a number of deleterious effects including cytotoxicity, immunotoxicity, and carcinogenesis. The mechanisms by which quinones produce these effects can be via alkylation of proteins and or DNA or by the formation of reactive oxygen species (ROS) that are generated by the redox cycling of quinones. Quinones can react with nucleophilic amino groups of DNA and proteins. Additionally, quinones react with sulfur nucleophiles (i.e., GSH and cysteine residues of proteins) leading to protein alkylation and/or GSH depletion. The generation of ROS leads to severe oxidative stress in cells via the formation of oxidized cellular macromolecules (e.g., DNA, proteins, and lipids) as well as activation of signaling pathways involved in the initiation, promotion, and progression of carcinogenesis. For more in-depth discussion on the subject of quinone chemistry and toxicology, the reader is referred to Monks et al. (1992) and Bolton et al. (2000).

As discussed, capsaicin may undergo bioconversion to a quinone - an activated metabolite having a multiplicity of deleterious effects. ROS formation and ROS-mediated lipid peroxidation are also quinone-mediated effects. Lipid peroxidation is associated with numerous pathological processes (Del Maestro, 1980; Recknagel et al., 1982) and has been the focus of considerable research. Timbrell (1982) has categorized the consequences of lipid peroxidation as secondary disturbances (e.g., membrane damage, enzyme inactivation) and tertiary disturbances (e.g., increased capillary permeability, protein cross-linking, reaction with SH, and decreased DNA synthesis). Peroxidation involves polyunsaturated fatty acids giving rise to free radicals and endogenous peroxides possessing high reactivity and cytotoxic properties. Lipid peroxidation is a reaction between fatty acids and oxygen, initiated by radical intermediates and active oxygen species, produced by metabolic processes or from metabolic conversion of xenobiotics. It is a process that may generate a broad range of lipid peroxidation products (Sevenian & Hochstein, 1985). Oxygen-derived free radicals are continuously produced in the cell during cellular metabolism as well as during the redox cycle of biochemical substances and antioxidant defense mechanisms are in place to minimize the harmful effects of these moieties. Free radicals are self-generating in a chain reaction and may be harmful to cells if protective mechanisms (e.g., α-tocopherol ascorbic acid, glutathione, antioxidant-enzymes such as catalase, and glutathione-related enzymes such as GSG-PX) are overloaded or not active (McCord & Fridovich, 1978).

Methyl radicals are reactive intermediates that are generated as a result of the metabolic conversion of capsaicin. O-demethylation of the 3-methoxy group on the vanillyl ring or O-demethylation of the phenoxy radical may generate the highly reactive methyl radical. O-demethylation generates the extremely reactive methyl radical, which is well-known to alkylate nucleic acids and proteins. The alkylation of proteins and/or GSH by electrophilic metabolites of capsaicin has consequences affecting cellular energetics, detoxification processes, as well as other biochemical processes. The potential of covalent binding with microsomal protein, for example, may account for the impact of capsaicin on xenobiotic metabolizing enzymes and liver toxicity. The interaction of methyl radicals are not limited to proteins and nucleic acids, these highly reactive moieties can also cause peroxidation of polyunsaturated and saturated lipids—the consequences of which have been previously discussed. In addition to the potential adverse effects resulting from the direct interactions of cellular constituents with the metabolic products of capsaicin, deleterious effects may result as a direct action of capsaicin on cellular processes, namely, cell bioenergetics. Concerning mitochondrial energy metabolism, Yagi (1990) postulated that capsaicin and dihydrocapsaicin produce repression of NADH-quinone oxidoreductase activity, which confirms findings suggesting capsaicin-induced inhibitory effects on hepatic mitochondrial bioenergetics.

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Appendix D - Supplemental Data on Capsaicinoids in the Context of Peripheral Sensory Irritants

This appendix was written by Dr. Bryan Ballantyne for use in this report. Portions of the text provided by Dr. Ballantyne have been incorporated into the main text.

Transient Changes in Intraocular Pressure (IOP) Following Local Ocular Exposure to Peripheral Sensory Irritants

In addition to causing structural injuries to the eye and its adnexa, local contamination of the eye with irritant materials can in some instances result in functional changes, some of which are pharmacologically induced, and which may have medical significance. One such effect is the induction of changes of pressure within the eyeball (intraocular pressure; IOP). This can be produced both by inflammation-inducing irritants and peripheral sensory irritants (Ballantyne et al., 1972). Many peripheral sensory irritant materials that cause an increase in IOP can also induce inflammatory changes, but often at much higher concentrations (Ballantyne, 1999a). The following discussion is limited to changes in IOP induced by peripheral sensory irritant materials that are used as riot control agents, or for smaller-scale self-protection devices (Ballantyne & Salem, 2004). The effects of these peripheral sensory irritants, principally 1-chloroacetophenone (CN), 2-chlorobenzylidene malononitrile (CS) and dibenz (b,f)-1,4-oxazepine (CR), on IOP has been studied both in laboratory animals and in controlled human exposures, the findings of which are briefly reviewed below.

Animal studies have been conducted in rabbits with CN, CS and CR and compared with a number of other general sensory irritants and inflammation-inducing chemicals (Ballantyne et al., 1972). In general, measurements were made by applanation tonometry (Ballantyne et al., 1977), before application of a small volume (approximately 0.1 mL) of solution to the eye, and then at 10 and 60 min post-application. With CN, there were clear concentration-related increases in IOP at 10 min for solutions in polyethylene glycol (PEG) 300 as follows: 0.0625% CN (7% increase), 0.125% CN (16%), 0.25% CN (19%), 0.5% CN (24%), 0.75% CN (49%), and 1.0% CN (98%). The increases in IOP were statistically significant at concentrations of 0.125% CN and higher. At 60 min post-application, the values had decreased to essentially control values, with the exception of 1.0% CN. At this concentration, the IOP at 60 min was markedly reduced compared to the measurements 10 min after application, but IOP was still statistically significantly increased compared to pre-application, at 13% (Ballantyne et al., 1975). With CS in PEG 300, there were also concentration-related increases in IOP at 10 min post-application but proportionally less than with CN. Based on concentration, increases were 0.125% CS (7%), 0.25% CS (10%), 0.5% CS (11%), 1% CS (30%), 2% CS (41%) and 5% CS (52%). Again, by 60 min post-application the pressures were down to control (pre-exposure) values, but with CS this occurred with all concentrations (Ballantyne et al, 1974). The studies with solutions of CR in PEG 300 also showed concentration-related increases in IOP at 10 min: 0.5% CR

(6%), 1% CR (20%), 2% CR (25%) and 5% CR (40%), with statistically significant rises at 1% CR and above. At 60 min post-application, pressures returned to control values with 1% CR; at the higher concentrations the pressures were still significantly increased, although much lower than at the initial application, with increases at 2% CR (9%) and 5% CR (11%) (Ballantyne et al., 1975).

The toxicological and practical relevance of these findings has been discussed in detail by Ballantyne (1999b). They indicate that materials with peripheral sensory irritant effects cause concentration-related increases in IOP, with a peak within a few minutes of the eye being exposed, and pressures returning to control values within an hour or so. These findings were confirmed in carefully controlled studies in human volunteers using solutions of CR in PEG 300. In one series of studies, 0.04 mL of solution (0.05% or 0.1%) was applied to one eye after measurement of IOP (by applanation tonometry) in both eyes. The IOP was then measured in the treated eye and the contralateral eye at 5 and 15 min, and at 3.5 and 24 h (Ballantyne et al., 1977); blood pressure was monitored simultaneously. With CR, the peak increase in IOP was measured at 5 min; with 0.05% CR, the peak increase was 40% in the treated eye and 16% in the contralateral (untreated) eye, and with 0.1% CR it was 44% in the treated eye and 17% in the contralateral eye. IOP in the contaminated eyes came down to control values by 3.5 h with 0.1% CR, and by about 15 min with 0.05% CR. IOP in the contralateral (untreated) eyes was at control values by 15 min with both concentrations of CR. The IOP changes are shown as a function of time and CR concentration, and compared with diastolic blood pressure (DBP) in Figure D-1. It can be seen that dilute solutions of CR applied to the cornea of human eyes causes a prompt increase in IOP, which returns to control values in 15 min with 0.05% CR and is sustained (up to around 3 h) with the higher CR concentration. In the contralateral eyes there are smaller increases in IOP, which are similar for both concentrations, and which follow the time course of transient increases in DBP. These findings suggest that the rise in IOP is due, in part, to a generalized systemic effect affecting both the treated and the contralateral eye. However the more marked and more sustained effect in the treated eye is due to a local ocular effect. Applied to the human eye, CR causes local pain and, as a consequence, an increase in systemic and central venous pressures. The increased central venous pressure will elevate episcleral venous pressure, and hence increase IOP in both the treated and untreated eye. It is, for example, well known that increase in IOP can occur secondary to the increased central venous pressure accompanying a Valsalva maneuver[1] (Grant, 1955). Accompanying the pain from the local peripheral sensory effect is hyperemia of the conjunctival blood vessels (Ballantyne et al., 1973a), and this congestion of the episcleral vessels will impair drainage of aqueous humor and further elevate the IOP. The human eye appears to be more sensitive to the ocular hypertensive effect of CR than is a standard laboratory animal model. For example, the application of 0.05% CR to the human eye caused a 40% increase in IOP at 10 min post-application, while the same

[1] This is a forced expiratory effort against a closed airway, such as closing the nose and mouth and blowing to inflate the Eustachian tubes when descending from high altitudes.

volume and concentration applied to the rabbit eye increased the IOP by only 4% over the same time period (Ballantyne et al., 1977).

Studies on the effects of PAVA and OC on IOP have not been conducted in either the laboratory animal or in humans by controlled studies or clinically following exposure in the context of crowd control activities. However, the fact that these materials cause both peripheral sensory irritant effects and, at higher concentrations, are capable of causing inflammatory/injurious effects on the eye, strongly suggests that OC and PAVA will produce typical prompt onset, short-duration ocular hypertensive effects.

From a medical perspective, the induced increases in IOP are generally briefly sustained and should not present any hazard to the majority of individuals. However, there is the possibility that those with incipient narrow-angle glaucoma may be precipitated into a first attack, and those with established glaucoma may experience an exacerbation (Ballantyne, 1977; Ballantyne et al., 1973b). Since the incidence of glaucoma is around 2% (Lyle et al., 1968) and because most of these cases occur in people over the age of 40 years (Smith, 1958), it is likely that, in the context of most civil disturbances in which peripheral sensory irritant riot control agents are used, the number of vulnerable individuals will be small. However, those responsible for the medical triage and management of individuals from a civil disturbance should be made aware of the potential for ocular hypertensive effects in the older population and that such subjects should be referred to have appropriate ophthalmologic screening. The only exception to the short duration of induced ocular hypertensive effects with peripheral sensory irritants is when the concentration in contact with the eye may cause ocular inflammation and injury. In these circumstances, there will be an initial increase in IOP, but with the onset of anterior segment damage the pressure will further increase and may be sustained (Ballantyne et al., 1973b, 1977).

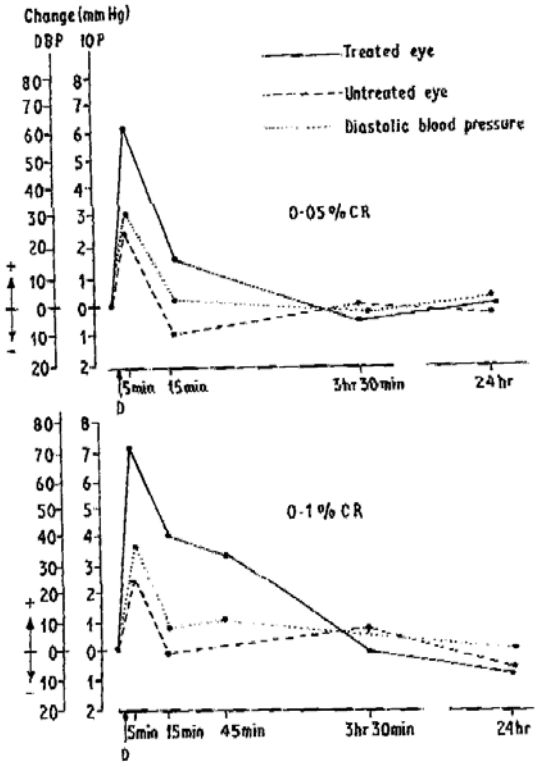

Figure D-1. Effect on intraocular pressure (IOP) of the human eye and of diastolic blood pressure (DBP) of solutions of dibenz(b,f)-1,4-oxazepine (CR) in a solvent of equal parts by volume of polyethylene glycol 300 (PEG 300) and water. A volume of 0.04 mL of either 0.05% or 0.1% was applied to one eye (treated eye). Average for 6 males in each treatment group.

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Early Cardiovascular Consequences of Exposure to Peripheral Sensory Irritants

Carefully controlled and conducted studies on human volunteers have shown that shortly after exposure to the peripheral sensory irritant materials 1-chloroacetophenone (CN), 2-chlorobenzylidene malononitrile (CS), and dibenz(b,f)-1,4-oxazepine (CR), there are increases in both systolic and diastolic blood pressure, often accompanied by reflex bradycardia. These cardiovascular changes have been noted following exposure to these chemicals as airborne irritants (aerosols or grenade-generated smokes), as dilute solutions (approximately 0.01-0.1%) topically applied to the eye, and as whole-body drenches of even more dilute solutions (0.001-0.005% CS, 0.001-0.0025% CR) (Ballantyne et al., 1976). The greatest amount of information and data has been obtained for whole body drenches, and this is presented in summary form below as being typical of cardiovascular responses to sensory irritants.

With the whole-body drenches (Ballantyne et al., 1976) using dilute solutions of CS and CR, there was immediate discomfort to the eye, blepharospasm, and profuse lacrimation lasting for 3-5 min. Skin sensations that developed very shortly after the eye irritation were described as stinging or burning; the cutaneous effects persisted on average for 5-10 min with CS and 15-20 min with CR. The shorter duration of symptoms with CS was probably related to its rapid hydrolytic inactivation in the dilute solution, and partly due to the lower intrinsic sensory irritancy of CS compared to CR (Ballantyne & Swanston, 1974). Accompanying the skin irritation with both CS and CR was an erythema with a distribution similar to that of the cutaneous irritation. However, the degree of erythema was not strongly correlated with the intensity of the sensation. Increases in blood pressure were first measured within a minute or so following irritant drenches and were moderate to marked. Thus with CR, peak increases in systolic blood pressure (SBP) ranged 30 to 70 mm Hg (mean 45 mm Hg) after 0.001% solution, and from 30 to 80 mm Hg (mean 59 mm Hg) after 0.0025%; some subjects had SBP increases to 200 mm Hg or higher. Peak increases in diastolic blood pressure (DBP) were 15-30 mm Hg (mean 23 mm Hg) with 0.001% CR, and 20-45 mm Hg (mean 20 mm Hg) after exposure to 0.0025% CR. The peak increases occurred between 1 and 3 min post-drenching, and were statistically significant for both concentrations of CR ($p<0.001$); thereafter, both SBP and DBP decreased to control (pre-drench) values. Times for DBP to return to within 10 mm Hg above control values ranged from 2 to 15 min; average time was 7.4 min for 0.001% CR, and 12 min for 0.0025% CR. Following drenching with 0.005% CS, the peak rises in SBP were 5-50 mm Hg (mean 31 mm Hg), and for DBP were 0-40 mm Hg (mean 19 mm Hg). Peak increases occurred between 1 and 2 min after drenching, and pressures returned to control values with 2 to 13 min of drenching. Increases in blood pressure persisted for periods comparable with the duration of irritant symptoms. Mechanistically, the increases in blood pressure could, at least in part, be (a) a consequence of a direct systemic pharmacological effect of absorbed sensory irritant, (b) a cold pressor effect of the drench itself, or (c) a result of the pain and discomfort coupled with apprehension. These possible causes are considered below.

A direct hypertensive effect of the sensory irritants seems unlikely for the following reasons. The onset in blood pressure rise is abrupt, and it is highly unlikely that sufficient amount of sensory irritant material could be absorbed percutaneously to exert a direct pharmacological effect over the 20-minute period that the pressures was elevated. Thus, with CR for example, *in vivo* and *in vitro* studies with rats using 0.005% CR dissolved in 3.3% dipropylene glycol monomethyl ether (DPM, the solvent system used in the drench studies) showed a steady state absorption rate of 300 pg cm-2 min-1; similar low values have been demonstrated with human skin *in vitro* (L. Leadbeater & H.N. Creasey, personal communication, 1975). Assuming a constant reservoir of CR on the skin, a 70 kg man of height 170 cm and body surface area of 1.8 m^2 would absorb CR percutaneously at a rate of about 5.4 µg min-1 from a 0.005% solution. Thus, over 20 min about 108 µg would be absorbed, equivalent to 1.5 µg kg-1 during this time. Studies in the cat have shown that the minimum dose of CR required to

produce a detectable pressor effect is 2.5 μg kg-1 when given as an acute rapid injection into the carotid artery (the most sensitive route of dosing). When given directly into the right atrium or aortic arch, doses of 62.5 μg kg-1 are required to produce a comparable pressor effect (D. Green & A. Muir, personal communication, 1975). Thus, the amount of CR that could be absorbed by a man over 20 min of exposure to 0.005% CR is highly unlikely to produce a measurable pressor response, even after accounting for interspecies differences. The rapidity of the blood pressure effect also argues against a direct hypertensive effect, since the peak increases in blood pressure occurred not later than 4 min after the onset of the drench, when only 22 μg (0.3 μg kg-1) could have been absorbed from a 0.005% solution. Additionally, in the cat studies 1.62 μg kg-1 infused intravenously over 1 h (corresponding to > 100 μg in a 70 kg man) produced a delayed SBP rise of only 20 mm Hg, indicating that the magnitude of the effect from systemic dosing of cats was somewhat smaller than that observed following the whole-body drenches of humans. Furthermore, the above calculations probably overestimate the actual amount of CR absorbed for a number of reasons, such as the assumption of a continuous reservoir, and because steady state conditions are not achieved until 30 min to 1 h after application. Similar toxicokinetic values apply to the effects of a CS solution on blood pressure (Brimblecombe et al., 1972).

To determine the possible contribution of a cold pressor effect, six volunteers in the same group as those drenched with irritant solution were subjected to a shower with cold water alone (Ballantyne et al., 1976). This produced a mean peak SBP increase of 32 mm Hg (range 0-85 mm Hg) and mean peak DBP increase of 7 mm Hg (range 0-25 mm Hg). Systolic pressures returned to control values within 2 to 3 min. These findings suggest that a pressor effect of cold drenching may contribute to a small extent towards the initial increases in BP, but the pressor effect is short-lived and cannot account for the more sustained increases in BP following irritant drenches.

Since the magnitude and duration of blood pressure increases was generally related to the degree of discomfort caused by the CS and CR drenches, it was considered appropriate to investigate the effects on blood pressure of another pain-inducing procedure. Thus, in a third phase of the Ballantyne et al. (1976) study, six volunteers had an ischemic pain test in which forearm muscles were temporarily deprived of their blood supply by the use of a sphygmomanometer cuff for 3 min (at 200 mm Hg), and were exercised by rhythmically squeezing a rubber cylinder. Blood pressures were measured in the contralateral arm. The procedure caused increases in both SBP and DBP; the increase in SBP at peak was 37 mm Hg (range 25-45 mm Hg) and in DBP was 26 mm Hg (range 15 to 40 mm Hg). The systolic rise caused by ischemic pain was significantly less than that caused by a 0.0025% CR drench ($p<0.001$) but not significantly different from that caused by drenches with 0.001% CR or 0.005% CS ($p<0.5$). However, there was no significant difference in the rise in DBP caused by ischemic pain and that caused by sensory irritant drenches. Subjectively the local ischemic pain was probably less unpleasant than the widespread severe discomfort produced by the irritant drenches. Based on the above considerations it is believed that the increases in blood pressure following irritant drenches were a

consequence of the intense and widespread cutaneous and ocular discomfort and pain, possibly coupled with apprehension.

Similar rapid-onset increases in blood pressure have been observed in controlled studies on volunteer subjects in which more concentrated solutions of CR (0.01-0.01%) were applied topically to the surface of the cornea, but the severity of the induced pain was greater than that resulting from the irritant drenches. It is likewise considered that the increased systolic and diastolic blood pressure following this procedure was primarily a result of pain induction in the eye (Ballantyne, 1977, 1988). Following exposure to irritant smokes there is a prompt increase in BP. For example, with CS smokes there were abrupt steep rises in systolic, diastolic and pulse pressures almost immediately after the removal of a protective respirator (Beswick et al., 1972). Thus for 27 volunteer subjects, the control (pre-exposure) mean systolic pressure was 123 mm Hg. Mean systolic pressure increased to 142 mm Hg on removal of the respirator and decreased to 124 mm Hg by 20 min; the corresponding respective values for diastolic pressure were 73 mm Hg, 84 mm Hg, and 75 mm Hg. Pulse pressures were 49 mm Hg pre-exposure, 57 mm Hg on respirator removal, and 49 mm Hg by 20 min. Heart rate (by EKG) decreased from 80 to 67 beats per minute (bpm). Thus the blood pressure changes appear to be related to the abrupt onset of ocular and respiratory discomfort.

The findings described above indicate that exposure to sensory irritants by airborne dispersion or skin contact with solution sufficient to produce moderately severe discomfort or pain results in abrupt increases in both SBP and DBP of a magnitude that may be tolerated without significant medical hazards in healthy individuals. However, as with other stressful situations, there may some individuals who may be susceptible to adverse consequences of increased blood pressure; this may include those with essential hypertension, established myocardial infarction, cardiac arrhythmias, and with diagnosed or occult aneurysms (Ballantyne, 1977, 1978; Ballantyne & Salem, 2004). Although the cardiovascular changes with OC and PAVA have not been well documented, particularly the early post-exposure effects, the fact that these materials are also peripheral sensory irritant materials and cause moderate to marked local discomfort, with associated reflexes, to the skin, eye and respiratory tract, indicates that the above conclusions regarding the genesis and pathophysiological significance of cardiovascular changes will also apply to OC and PAVA.

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Complications from the Use of Soft Contact Lenses

There are differences of opinion on the advantages and disadvantages of wearing soft contact lenses during exposure to irritant materials. These differences are due, in part, to variable emphases on the opposing effects of shielding by the contact lens and increased contact time from the material becoming trapped beneath the lens and in contact with the cornea. It has been stated in connection with trials using CS aerosol generators that individuals wearing soft contact lenses kept their eyes open more easily and had quicker and better orientation (Aalphen et al., 1985). A limited account described two police officers who wore soft contact lenses in training drills with CN and CS and who were able to conduct their duties effectively without ocular complications (Aalphen et al., 1985). Conversely, other authorities believe that the use of soft contact lenses could result in visual problems relating to both the irritant and/or other formulation constituents, and the adverse or protective effects could vary with the chemical and physical nature of the sensory irritant (Ballantyne & Salem, 2004). It has been noted that hydrophilic soft contact lenses may absorb chemicals secondarily to their network structure, and thus be a source of prolonged exposure and enhance local toxicity (Loriot & Tourte, 1990). Thus, soft contact lenses may cause entrapment of material under the lens and increase contact time with the cornea; this may facilitate injury from irritant or formulation components. In this respect it has been specifically noted that soft contact lenses contaminated with OC may adsorb the material and it may be difficult to remove residual OC (Lee et al., 1996); thus, contaminated lenses should be discarded. Additionally it has been

noted that some solvents in irritant solution formulations may lead to solubilization and/or fragmentation of soft contact lenses (Ballantyne, 2005), or to hardening of soft contact lenses (Holopainen et al., 2003). This may lead to increased irritation and to superficial corneal injury, which may be enhanced by the manual rubbing of the eyes that characteristically accompanies topical sensory irritation of the eyes. It is generally recommended that soft contact lenses should not be worn during the dispersal of irritant solutions, and that decontamination procedures should include removal of contact lenses to ensure adequate irrigation of the eye.

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Appendix E - Approach for Respiratory Effects Conversions

General Approach

This Appendix summarizes the approach used to convert among dose measures for respiratory effects, with a focus on the studies used as the basis for the threshold.

As described in Section 3, the best dose metric for peripheral sensory irritant effects is the concentration to which the tissue is exposed. While determination of the concentration in the tissue itself in the region of sensory nerve receptors would be ideal, sufficient information was not available to determine that value. The next best approach for a gas is to use the concentration in the inhaled air in the appropriate region of the respiratory tract. For aerosol droplets, one needs to take into account the relative deposition in various regions of the respiratory tract, and calculate the mass of material deposited in the major respiratory regions.[2] This calculation takes into account the particle size and the differences in deposition in different regions. These parameters are also likely to be more dependent on the chemical than the species, so this approach also is a reasonable approximation to the extrapolation from controlled studies in animals, given the available data. Ideally, calculations would also take into account the concentration of capsaicin in the inhaled air, but the studies did not provide sufficient information to calculate that value.

Therefore, the first step in calculating deposited doses was to determine the amount of inhaled material. Some studies provided that information directly. Others provided the concentration of capsaicin in the aerosol and the volume inhaled. This allowed the amount inhaled to be calculated using the equation:

Amount inhaled (µg) = concentration of capsaicin in solution (mg/L)/(1000 mL/L)x volume inhaled (mL) x 1000 µg/mg

Some studies provided the concentration in µM. This was interconverted with mg/L using the equation:

Concentration (µM) = concentration (mg/L) x 1000 /(305.4)

Where 305.4 is the molecular weight of capsaicin

And the factor of 1000 is to convert g to mg and M to µM

Some studies did not provide the volume inhaled, but provided information on the flow rate of the nebulizer and the duration of exposure. For these studies, the amount inhaled was calculated using the following equation:

[2] As described by U.S. EPA (1994), these regions are (1) the extrathoracic (ET) region (called head region by the MPPD model described below), including the nose, mouth, laryngopharynx, and larynx; (2) the tracheobronchial (TB) region, including the trachea, bronchi, and bronchioles; and (3) the pulmonary (Pu) region, including the respiratory bronchioles, alveolar ducts and sacs, and alveoli.

Amount inhaled (μg) = aerosol concentration (mg/L)/(1000 mL/L)x duration (min) x flow rate (mL/min) x 1000 μg/mg

This approach assumes that all nebulized material was inhaled. While this may be a slight over-estimate of the amount inhaled, it is a reasonably good assumption for an apparatus with small dead space, as appeared to be the case for these systems.

One challenge in the calculation of the inhaled mass was that the only relevant information provided in many of the cough and bronchoconstriction studies was the concentration of the nebulized solution and the duration of exposure. In the absence of sufficient information to calculate inhaled mass, the first approach was to determine whether other studies by the same authors provided such information, and whether other studies using the same nebulizer provided flow rate information. In the absence of such information, it was assumed that the flow and exposure duration of Midgren et al. (1992) were used. This was a semi-arbitrary choice, based on the study quality and documentation, and because the protocol used seemed fairly typical. The impact of this assumption could not be determined, since other studies reported both higher and lower flow rates.

Results of the calculation of the mass inhaled are shown in Table E-1 for the studies and endpoints relevant for determination of thresholds in this assessment.

Table E-1. Calculation of the mass inhaled for studies relevant to threshold determinations

Study	Aerosol Concentration		Duration (min)	Flow Rate (mL/min)	Volume Inhaled (mL)	Amount Inhaled (µg)	Effect
	µM	mg/L					
Blanc et al. (1991)	3	0.92	0.05[c]	NS	0.013	0.012	One capsicum worker had >20% decrease in FEV1
	6	1.8	0.05[c]	NS	0.013	0.024	Lowest concentration at which all subjects coughed
Cho et al. (2002)	250	76	0.05[c]	0.5[a]	NS	1.9	No bronchoconstriction in normal or asthmatic subjects
Collier and Fuller (1984)	4	1.2	1	0.5[a]	NS	0.61	All subjects coughed
Doherty et al. (2000)	31	9.5	NS[c]	13	0.009	0.085	Median cough threshold (C5) in subjects with chronic obstructive pulmonary disease (COPD)
	62	19	NS[c]	13	0.009	0.17	Median cough threshold (C5) in asthmatics
	500	**150**	**NS[c]**	**13**	**0.009**	**1.4**	**Cough threshold (C5) reached in approximately 45% of normals**
Fujimura et al. (1993)	8	2.4	0.25	0.21	NS	0.13	Cough threshold (C5) caused no bronchoconstriction in normal subjects, or in subjects with asthma or bronchitis
Fuller et al. (1985)	10	3.1	1	NS	NS	0.073[b]	Decreased specific airway conductance
Hathaway et al. (1993)	**1**	**0.3[d]**	**1**	**0.5[a]**	**NS**	**0.15**	**Highest concentration not causing bronchoconstriction in any subject**
	10	3[d]	1	0.5[a]	NS	1.5	Lowest concentration causing bronchoconstriction (>20% decrease in FEV1) in asthmatics
	1000	300[d]	1	0.5[a]	NS	150	No bronchoconstriction in normal subjects
Ind et al. (2001b)	3300	1000	NS[c]	NS	0.006	6	No significant decrease in FEV1 in asthmatics
Midgren et al. (1992)	10	3.1	1	0.5	NS	1.5	Lowest concentration at which all subjects coughed

[a]Value not reported, assumed the value reported by Midgren et al. (1992)
[b]Fuller et al. (1985) reported the amount of chemical inhaled.
[c]Single breath study
[d]Original units
NS = not stated
Data used for thresholds are bolded

The second step in calculating regional deposited doses was to determine the deposition fraction (the fraction of the inhaled mass that is deposited in each region of the respiratory tract), for the aerosol droplet size distribution in the study. Two software packages were considered for this. The U.S. EPA guidance for calculation of reference concentrations (U.S. EPA, 1994) includes the RDDR (regional deposited dose ratio) program. This is a well-established program for calculating the deposition fraction, but is limited in that it is empirically based. The other software program, MPPD (Multipath Particle Deposition, available from B. Asgharian, CIIT) has the advantage of being mechanistically-based. In addition, while RDDR assumes humans breathe through their noses, except at high ventilation rates, the MPPD program allows one to specify oral, nasal, or oronasal breathing. This last factor was important because almost all of the human studies (i.e., using nebulizers) were conducted using oral breathing scenarios.

Calculation of the deposition fraction requires information on the aerosol droplet size distribution, characterized as the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD). When both numbers were provided, they were used directly in the program. Similarly, since the aerosol density was assumed to be close to 1, the mass median diameter was taken as the MMAD. When no information was provided, a MMAD of 3 μm and a GSD of 3 μm was assumed, as a rough generalization of nebulizer characteristics. A GSD of 3 μm was also assumed if only the MMAD was available. For some studies, only the range was available. In such cases, the upper end of the range was often lower than the MMAD reported by other studies, so it was not appropriate to estimate the MMAD based on other nebulizers. In the absence of a better approach, the MMAD was estimated by taking the geometric mean of the extremes of the range. This approach ignores the mass-weighting, and so under-estimates the MMAD. Sensitivity analyses (shown using RDDR for the Reilly et al., 2003a study) indicated a difference of maybe 50% in the resulting deposition in the region of interest (TB) when using this approach rather than a rough estimate from the upper end of the distribution.

If the range was reported, but not the GSD, the GSD was calculated using the formula, as described by U.S. EPA (1994):

GSD = exp [ln (median/lower bound)/n] or
exp [ln (median/upper bound)/n]

(The same value should result using both approaches.)

Where

Exp is the irrational number, e, raised to the power in brackets

And “n” is a parameter reflecting the number of standard deviations used in calculating the GSD. Thus, if 68% of the droplets were in the reported range, n=1, if 95% are in the reported range, n=2, if 99.7% are in the reported range, n=3, and if >99.99% are in the reported range, n=4. Where the percentage in the range was reported, that was used to determine n. Otherwise, it was assumed that 99.7% were in the reported range.

The final information needed to determine deposition fraction is the tidal volume (and associated breathing frequency). For the studies involving multiple

breaths using tidal breathing, the default parameters of the model were used (tidal volume of 625 mL and breathing frequency of 12/min). However, no adjustment could be made for interruptions of the breathing cycle by capsaicin-induced coughing. Coughing would mean that the pulmonary dose (and perhaps other doses) would be over-estimated.

It was less clear how to address tidal volume and breathing frequency for single-breath studies, particularly when it was noted that subjects were asked to breathe deeply. For studies reporting tidal breathing for that single breath, or in the absence of other information, a single breath was assumed to take 1/12 of a minute (based on 12 breaths/min), and the default tidal volume was assumed. Sensitivity analyses (e.g., as shown for the Blanc et al., 1991 study) conducted to evaluate the impact of varying the tidal volume and breathing frequency indicated that these uncertainties had a much smaller impact on the estimate of deposited dose than the uncertainties regarding aerosol drop size distribution or volume inhaled.

The final step in calculating deposited dose is to multiply the deposition fraction by the amount inhaled.

Regional deposited dose (μg) = Regional deposition fraction x amount inhaled (μg)

The results of these calculations are shown in Table E-2.

Table E-2. Calculation of Deposited Dose for Studies Relevant to Threshold Determinations

Study	MMAD (μm)	GSD (μm)	Fraction Deposited			Aerosol Concentration (μM)	Deposition (μg)			Comments
			Head	TB	PU		Head	TB	PU	
Blanc et al. (1991)	3	3	0.21 - 0.24	0.18 - 0.21	0.25 - 0.27	3	0.0025 - 0.0029	0.0021 - 0.0025	0.0032 - 0.003	
	3	3	0.21 - 0.24	0.18 – 0.21	0.25 - 0.27	6	0.0051 - 0.0058	0.0043 – 0.0049	0.0059 - 0.0063	1, 4, 6, 7, 10
Cho et al. (2002)	3	3	0.22	0.19	0.27	250	0.42377	0.368413	0.523032	1,4,7
Collier and Fuller (1984)	4.5	1.3	0.7	0.091	0.13	4	0.43	0.056	0.079	2,5,12
	3.7	1.2	0.63	0.092	0.17	4	0.38	0.056	0.1	3,5,12
Doherty et al. (2000)	**5.2**	**3**	**0.24**	**0.34**	**0.24**	31	0.021	0.029	0.021	
						62	0.042	0.058	0.041	
						500	**0.34**	**0.47**	**0.33**	4,9
Fujimura et al. (1993)	3	3	0.23	0.22	0.18	8	0.029	0.028	0.023	1,4
Fuller et al. (1985)	3.7	3	0.26	0.25	0.16	10	0.019	0.018	0.012	2,4
Hathaway et al. 1993						**1**	**0.034**	**0.033**	**0.027**	
						10	0.34	0.33	0.27	1,4,10
	3	**3**	**0.23**	**0.22**	**0.18**	1000	34	33	27	
Midgren et al. (1992)	3	3	0.23	0.22	0.18	10	0.35	0.33	0.27	4
	1.3	**1.7**	**0.18**	**0.105**	**0.127**	**625**	**113**	**66**	**79**	
Reilly et al. (2003a)	**2**	**1.7**	**0.355**	**0.086**	**0.139**	**625**	**222**	**54**	**87**	**11**

Inhalation was mouth-only in human studies, unless otherwise noted. Data used for thresholds are bolded

Comments:

1 - Assumed MMD = 3 μm
2 - Assumed MMD or MMAD = geometric mean of reported upper and lower estimates of the range
3 - Assumed MMD = MMD reported for other studies in the same lab
4 - Assumed GSD = 3 μm
5 - Estimated GSD from the reported range of diameters using the method of U.S. EPA (1994)
6 - Doubled tidal volume to 1250 mL to simulate deep breathing
7 - Doubled tidal volume to 1250 mL and reduced breathing frequency to 10 breaths/min, to simulate deep breathing
8 - Increased tidal volume to 1000 mL and reduced breathing frequency to 10 breaths/min, to simulate deep breathing
9 - Doubled tidal volume to 1250 mL and reduced breathing frequency to 6 breaths/min, to simulate slow, deep breathing
10 - Aerosol concentration reported as mg/L. Converted to μM and rounded for this table, but calculations done using concentrations in Table E-1
11 - Dose from rat study, reported as total inhaled dose
12 - Inhalation via face mask

Example calculations for Critical Thresholds

Cough Threshold

Based on the study of Doherty et al. (2000), the concentration of interest is 500 μM in the solution that was nebulized.

500 μmol/L x MW 305 for capsaicin = 150 mg/L

The nebulizer output was not reported, but the amount inhaled in the single-breath study was reported as 0.009 mL.

Therefore, **inhaled dose = 150 mg/L x 0.009 mL x 1L/1000 mL = 0.0014 mg = 1.4 μg**

The mass median diameter of the aerosol was 5.2 μm. In the absence of data on the GSD, a GSD of 3 was assumed. According to the MPPD program, this distribution results in fractional deposition to the head, tracheobronchial and pulmonary regions of humans of 0.24, 0.34, and 0.24, respectively.

To calculate the regional deposited dose, the regional fractional deposition is multiplied by the inhaled dose.

Dose to the tracheobronchial region = **1.4 μg x 0.34 = 0.47 μg**

This was rounded to **0.5 μg**, in light of the numerous uncertainties

Bronchoconstriction Threshold

Based on the study of Hathaway et al. (1993), the concentration of interest is 0.3 mg/L in the solution that was nebulized. The exposure duration was reported as 1 min, and the flow rate reported by Midgren et al. (1992) of 0.5 mL/min was used in the absence of other available data.

Therefore, **inhaled dose = 0.3 mg/L x 1 min x 0.5 mL/min x 1L/1000 mL = 0.00015 mg = 0.15 μg**

The MMAD and GSD were not reported, so the default of 3 was used for both values. According to the MPPD program, this distribution results in fractional deposition to the head, tracheobronchial and pulmonary regions of humans of 0.23, 0.22, and 0.18, respectively.

To calculate the regional deposited dose, the regional fractional deposition is multiplied by the inhaled dose.

Dose to the tracheobronchial region = **0.15 μg x 0.22 = 0.033 μg, rounded to 0.03 μg**

Pulmonary Effects Threshold

A comparable approach was used for the animal data, except that the starting point used for the inhaled dose was the internal dose calculated by the study authors. The inhaled dose was back-calculated from that amount, and then the deposition fractions were calculated in order to determine the regional deposited dose. In addition, since normal breathing was assumed, the U.S. EPA (1994) RDDR program was used to calculate deposition fractions, as a simpler and well-established approach.

Based on the study of Reilly et al. (2003a), the dose of interest is 0.5 mg/kg. This dose was calculated by the study authors as the deep lung deposited dose, based on a 10% deposition fraction. The body weight of the rats was reported as 125 g.

The total deposited dose was calculated as **0.5 mg/kg x 0.125 kg = 0.0625 mg**

Since this dose was based on an assumption of 10% deposition, it was divided by 0.1 to determine the total inhaled dose.

Inhaled dose = **0.0625 mg / 0.1 = 0.625 mg = 625 μg**

The particle size was reported as <0.6 – 2.9 μm. As an estimate of the MMAD the geometric mean of the range was calculated, and found to be 1.3 μm. A sensitivity analysis was conducted by also using an MMAD of 2 in the calculations, to estimate the impact of not weighting by mass in estimating the MMAD. Based on 85-90% of the droplets being in the range, the GSD was calculated using the equation described above, and n=1.5. For MMAD = 1.3 μm and GSD = 1.7 μm, the RDDR program calculates fractional deposition to the tracheobronchial and pulmonary regions of a 125 g rat as 0.105 and 0.127, respectively.

To calculate the regional deposited dose, the regional fractional deposition is multiplied by the inhaled dose.

Dose to the pulmonary region = **625 μg x 0.127 = 79 μg**

As shown in Table C-2, for MMAD = 2 μm and GSD = 1.7 μm, the pulmonary deposition fraction is 0.139, and a dose of 87 μg results. In light of the uncertainties, the averaged and rounded dose of 80 μg was used to calculate the threshold.

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Appendix F - Modeling Flammability of OC Sprays

The solvents reported by Conrad (2004) that are typically used in OC sprays are isopropanol, ethanol, sec-butanol, propylene glycol, dipropylene glycol methyl ether, and d-limonene[3]. The potential for flammability of OC mixture containing the solvents was determined using the conservative approach of determining if the mixture will produce a concentration of solvent in air that exceeds the Lower Explosive Limit (LEL) of the solvent under conditions of saturation. This determination is then used to specify a minimum concentration of the solvent in water that can produce a concentration equal to the LEL.

This concentration was determined for each of the solvents using the following process. First, it is assumed that the properties of explosivity and ignitability are the same. Thus, the flammability of the subject solutions is assumed to occur when the vapors of the solvent above the solution are capable of reaching the Lower Explosive Limit (LEL) concentration; that is, when the solvent vapors at saturation concentrations above the solution have a concentration that is at or above the LEL. The LELs for all of the solvents are available from the literatures (see Table F-1).

Table F-1. Physical Chemical Values Used in Calculations.

COMPOUND	LEL (%)	ref	VP (torr)	ref	MW (g/mole)	ref	BP (°C)	ref	Thermodynamic Activity $\propto$ @ 50 mole% in H_20 (25°C)	ref
ethanol	3.3	2	60	1	46.1	1	78	1	1.20	11
isopropanol	2.0	3	44	3	60.1	3	82	3	1.24	11
sec-butanol	1.7	4	18.3	5	74.12	4	94	4	1.26	11
propylene glycol	2.6	6	0.129	6	76.09	6	188.2	6	NA*	-
DPM glycol	1.1	7	0.28	7	148.2	7	190	7	NA*	-
d-limonene	0.7	9	2	9	136.26	8	154	9	NA*	-
water	NA	-	22	10	18	10	100	10	NA*	-

* : 100% solvent used in flammability analysis therefore: $\propto$ = 1.00

1. http://www.arb.ca.gov/db/solvents/solvent_pages/Alcohols-HTML/ethanol.htm
2. http://www.carolina.com/stcms/acrobat/stc_msds/POM_MSDS/Ethanol.pdf
3. http://www.jtbaker.com/msds/englishhtml/i8840.htm
4. http://www.jtbaker.com/msds/englishhtml/b6302.htm
5. http://www.jtbaker.com/msds/englishhtml/b6302.htm

[3] d-limonene has limited water solubility and is likely added with other solvents.

6. http://www.jtbaker.com/msds/englishhtml/p6928.htm
7. http://www.dow.com/PublishedLiterature/dh_0411/09002f13804111f2.pdf?filepath=/PublishToInternet/InternetDOWCOM/msds/SDS_00022345_DOWANOLDPM_UNITEDSTATES_ENGLISH&fromPage=MSDS
8. http://www.arb.ca.gov/db/solvents/solvent_pages/Hydrocarbon-HTML/d-limonene.htm
9. http://www.safe-react.com/msdsdlim.htm
10. http://hyperphysics.phy-astr.gsu.edu/hbase/kinetic/watvap.html#c1
11. http://www.hsrc-ssw.org/ssw-downloads.html

Second, the saturation concentration of a solvent in the presence of an OC spray is based on the vapor pressure of the solvent from the spray mixture. Raoult's Law is used as a starting point for characterizing the vapor pressure of the solvent. This relationship is as follows:

$$VP_{solution} = (VP_{Pure})(Mole\ Fraction) \quad (1)$$

$VP_{solution}$ = the vapor pressure of the solvent above the solution (torr)
VP_{Pure} = vapor pressure of the pure solvent (torr)
Mole Fraction = fraction of the total moles in the solution that is the solvent (unitless).

The values of the solvent vapor pressures are given in Table D-1.

Third, since many water organic solvent mixtures do not follow Raoult's law, Equation 1 was modified to include a term that describes the variation for ideal behavior of the mixture. The revised equation is:

$$VP_{solution} = (VP_{Pure})(Mole\ Fraction)(\alpha) \quad (2)$$

α = Thermodynamic activity coefficient

The thermodynamic activity coefficient is estimated using a complicated physical-chemical model known as UNIFAC (Fredenslund et al., 1975). The method includes a lengthy procedure unsuitable for situations where a quick and simple calculation is required. To make the UNIFAC method easily accessible for quick calculations, the UNIFAC Activity Coefficient Calculator was developed (UNIFAC, 2004)[4]. UNIFAC uses molecular structural activity relationships and, since the thermodynamic activity coefficient is not constant but a function of concentration, it also uses the mole fraction of the various solvents in the solutions to calculate the coefficients for each.

Once these values have been identified, the following process was used to derive the lower bound of the level of a solvent in water that will produce a saturation air concentration of solvent above the LEL.

[4] The calculator is a 32-bit Windows 95 or Windows NT application that applies a user-friendly interface to the UNIFAC method. The system's chemical species are chosen from pull-down lists. The chemical component database is fully customizable, and allows for the creation and editing of species using the UNIFAC subgroup definitions.

Step 1: Determine the molecular weight (MW), LEL, and VP_{Pure}, for the solvent under consideration.

Step 2: Calculate the saturation concentration for the pure solvent from the following relationship:

$$C_{SAT} = \frac{VP_{Pure}}{760}(1,000,000) \quad (3)$$

C_{SAT} = saturation concentration (ppm v/v)

This is compared to the LEL expressed as ppm v/v (i.e., (LEL%)(10,000))

IF the C_{SAT} < LEL then the solvent (even without dilution) is not flammable using the above definition.

IF C_{SAT} > LEL go to Step 3:

Step 3:

Assume a 50wt % solution of the solvent in water and calculate:

1. The mole fraction of water and the solvent in the solution.
2. The Thermodynamic Activity Coefficient of the Solvent using UNIFAC at this mole fraction for the water and solvent.
3. The resulting $VP_{solution}$ of the solvent using the above Equation 2.
4. C_{SAT} using Equation 4 below.

$$C_{SAT} = \frac{VP_{solution}}{760}(1,000,000) \quad (4)$$

IF C_{SAT} < LEL then increase the concentration of the solvent to 75% and repeat Step 3.

IF C_{SAT} > LEL then decrease the concentration of the solvent to 25% and repeat Step 3.

Repeat Step 3 until a wt% with a C_{SAT} that is equal to the solvent's LEL is identified. This value is the threshold concentration of flammability for this solvent in water.

This process was performed on isopropanol, ethanol, sec-butanol, propylene glycol, dipropylene glycol methyl ether, and d-limonene. Isopropanol is the most flammable based on these combinations of properties and may be flammable down to 10% in water. This low level of concentration is due to the low

value of the LEL for the compound (20000 ppm v/v) it high vapor pressure (44 torr) and the fact that the thermodynamic activity coefficient is predicted to go up rather dramatically as the concentration of isopropanol goes down in water. Ethanol is predicted to be flammable down to about 40% concentration in water. Sec-butanol is predicted to be not flammable below 85% in water. Propylene glycol, dipropylene glycol methyl ether, and d-limonene are not flammable at room temperature even as pure materials and therefore do not present any risk of flammability.

The temperature used in this assessment is 25°C. During the summer months and in instances where the temperature of the clothing has been elevated from body heat or some other source of heat the spray may be at a higher temperature. At higher temperatures the fraction of the solvent in water that is flammable will decrease. This will affect the estimates of the minimal concentrations for ethanol, isopropanol, and sec-butanol. It will not affect the findings for propylene glycol, dipropylene glycol methyl ether, and d-limonene since their vapor pressures are well below the LEL.

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Appendix G - Modeling Stream and Cone Sprays

Modeling Exposure to OC Sprays Using a Physics-Based Model of Individual Droplets

Concept

The OC devices operate by the creation, movement, and interaction of droplets with the target individuals. The characteristics of the droplets determine the movement through air, the potential for changing size, and the ability to interact with the target individual.

Because of the importance of the droplet behavior to characterizing exposure, a model was constructed based on the simulation of individual droplets. In developing this model, variants were required to address the different types of OC devices. The streams and cone sprays could be handled in a model that tracks the position of the droplet in space over time. This model is based on the concept that the movements of larger droplets are largely determined by the kinetic energy in the droplets, wind resistance, and gravity[5]. The model does not consider the effect of evaporation since the droplets are airborne for only a few seconds, a period too short to allow for significant evaporation of solvents. The model also does not consider the impact of droplet collision and the formation of larger droplets. Because the droplets are in an expanding jet stream the droplets will disperse over time and distance. This dispersion will minimize droplet-droplet interactions[6].

The model operates over brief periods of time (<2 s) and ends when the droplet strikes the individual, passes the individual, or strikes the ground. The approach used is to model the droplets using a discrete set of time steps. The droplet has a specific location at each point in time defined by a Cartesian grid (*X,Y,Z*). The time steps are short, one thousandth of a second. At the end of each time step the droplets' location and velocity are determined.

The Framework

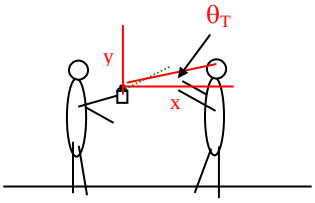
The framework for the cone spray/stream model (hereafter the model) is based on the user and target individual facing each other within a distance of from 0.5 to 5 m. The user holds an OC device that emits droplets at a given velocity. The nozzle is aimed at the target individual's head. This aiming takes into account the effects of gravity. X is the horizontal distance between the device and the target individual; Y is the height of the target face relative to the device. Z is the

[5] The effects of aggregate jet stream effects, eddy diffusion, and evaporation of particles were evaluated for the model. For the time period modeled (1-2 seconds) and the size of the particles (> 50 μm) these process have a minimal effect.

[6] Droplet to droplet impacts are possible since drag will cause smaller droplets to slow down faster then larger droplets thus larger droplets can catch up with smaller droplets. This factor is not considered in the model.

axis at right angles to X and Y. The following figure shows the coordinate system (Z is the axis in and out of the paper).

Figure G-1. Distance from User to Target Individual.



The model allows the user to specify different distances between the user and the target. The location of the device is defined as the origin of the coordinate system. Thus, all droplets begin at a location of (0,0,0). The device is pointed in such a way that droplets in the center of the spray will strike the face of the target. The aiming of the device is determined by the tilt angle (θ_T). θ_T is defined as the angle from horizontal to the center of the spray, see Figure G-1. The target (the individual's face) is defined as being centered on the location (X, H, 0), where X is the distance between the device and the target individual and H is the height of the center of the target individual's face above the device. In this model, the wind is assumed to be very low.

Modeling Droplet Creation

Droplets are formed at or near the nozzle of the spray device. The user specifies a distribution of diameters for the droplets. The droplets are assumed to be spherical. The user also defines the characteristics of the spray mixture. This includes the density of the OC, the total amount of OC and capsaicinoids, and the density of the spray mixture.

The user provides a nozzle velocity. All droplets are assumed to have the same initial velocity. The droplets are assigned a direction of movement. This direction is defined by the three vectors[7] of the velocity (x,y,z).

The direction of the droplets is defined in terms of the following:

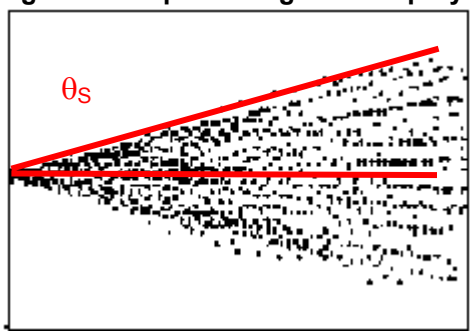
- The tilt angle of the device (θ_T);
- The spread angle of the spray (θ_S); and
- An assumption that there is a uniform density of droplets across the spray.

The spread angle θ_S is the angle from the outer edge of the spray to the center of the spray; see the figure below. Both θ_S and θ_T are entered by the user.

[7] Velocity vectors will be identified by using bold numbers.

The spread angle θ_S is the factor that differs the most between the stream and cone sprays. Based on a visual examination of the cone and stream as demonstrated by the manufacturer, the value of θ_S is estimated to be 20° for the Brand Y Cone and 0.23° for the Brand X Stream.

Figure G-2. Spread Angle for a Spray.



The model then uses simple trigonometry to define the values for the velocity vectors (x,y,z), based on the angles θ_S and θ_T.

Modeling Movement

The location of the droplet in space[8] (*X,Y,Z*) at a point in time is determined based on the location at the beginning of the prior time step plus the velocity times the duration of the time step (TS). Thus, if the location at the beginning of the prior time step is (*0,0,0*) and the velocity vectors are (1,1,0) and TS is 0.001 then:

At Time = 0

X = 0
Y = 0
Z = 0

or

(*0,0,0*)

At Time = 0.001

X = 0 + **x** * TS = 0 + 1 * 0.001 = 0.001
Y = 0 + **y** * TS = 0 + 1 * 0.001 = 0.001
Z = 0 + **z** * TS = 0 + 0 * 0.001 = 0

or

[8] Locations are described as capitals and italics.

(*0.001,0.001,0*)

The velocity of the droplet changes with time. The values for (**x,y,z**) are affected by the forces that are exerted on the droplet by wind resistance (drag) and gravity.

The change in velocity in a time step is given by:

$\Delta\mathbf{x} = TS * A_x$
$\Delta\mathbf{y} = TS * A_y$
$\Delta\mathbf{z} = TS * A_z$

Gravity accelerates the droplet in the y direction. This effect is described by:

$A_y = -9.8\ m/sec^2 * TS$

The effect of drag is calculated by determining the force exerted on the droplet. F_D for droplets > 50 μm is given by:

$F_D = \frac{1}{2} C_D \rho v^2 A$

where,

C_D is the drag coefficient. For spherical droplets the value of C_D is 0.5 (Serway & Jewett, 2003).
ρ is the density of air at 70° F.
v is the total velocity of the droplet at the beginning of the time step.
A is the cross sectional area of the particle at the beginning of the time step.

The acceleration from this force (A_D) is given by:

$A_D = F_D / M_D$

where:

M_D is the mass of the droplet.

Since the direction of the force is opposite to the direction of the velocity, A_D can be decomposed into three corresponding vectors of acceleration A_{Dx}, A_{Dy}, and A_{Dz}.

Therefore

$\Delta\mathbf{x} = TS * A_{Dx}$
$\Delta\mathbf{y} = TS * (A_{Dy} - 9.8\ m/sec^2)$
$\Delta\mathbf{z} = TS * A_{Dz}$

Using these equations, the trajectory of the droplets can be defined as a series of points in space over time. These data can be used to answer questions as to how far the droplets will travel and the trajectory of the droplets.

The model suggests that droplets of less than 100 μm will travel less than 1 m before drag forces stop any forward progress. In order to reach distance greater than 5 m, droplets must be in the 1,000 to 3,000 μm size range.

The model predicts that the PAVA product will have a range in still air of 5 to 6 m. This agrees with the descriptions of the effective distance provided by the manufacturer. The model's predictions were also compared against direct measurements of the PAVA Stream in a small test performed by LINEA, Inc. A training version of the PAVA Stream (containing only water) was fired in a horizontal direction and witness boards were set up at two distances 2.5 m and 4.4 m in an indoor environment. The centers of the steam impact on the boards relative to the height of the nozzle were measured in cm. The model was run assuming a value of θ_T of zero. The vertical drop of the stream at the two distances was calculated for 100 droplets. Table G-1 reports the results for the model prediction and the observations.

Table G-1. Observed and Modeled Changes in Elevation of Steam at Two Distances.

Distance from Device (m)	Observed Drop in Stream (cm)	Predicted Drop (cm)
4.4	-0.64	-0.68
2.5	-0.16	-0.152

Modeling Droplet Interactions with Individuals

The targets of interest for the model are the target individual's eyes and mouth. The interaction between the droplets and these targets are defined in a two-step process. First, the model determines if the trajectory will result in an impact with the face. Second, the model determines if the droplets strike the eye or the mouth.

The first step was performed differently for the two products. As discussed in the exposure section, streams are assumed to be aimed in such a way that the majority of the stream will strike the face some fraction of the time. This aiming and the volume of spray material that hits the face, mouth, and eyes is determined directly and not by modeling individual droplets. However, as discussed below, the model was used to estimate droplet velocity at the eye for the stream products.

In the case of the cone spray, the model is used to determine eye impact. This was performed by testing each time step on the droplets' trajectories to determine if the droplets had crossed the location of the face. The location of the face was defined as a circle 12 cm in radius with a center at (*X,H,0*) that faces (is right angles to) the device. The value of X is the distance between the device and the target individual and the value of H is the height of the center of the target individual's face above the device. If the droplet has a location at a time step that is in front of the face and at the next time step has a location behind the face, then

the droplet is defined as striking the face at the first time step[9]. The velocity of the droplet at this location is saved.

Once the model determines that a droplet strikes the face, the probability that the droplet strikes an eye is determined based on the relative sizes of the eye and the face. If a droplet is determined to strike the eye, then the volume of the droplet is used to determine the dose to the eye. The velocity of the droplet is used to determine the risk of pressure injury.

As discussed in the exposure section of this report, the amount of a stream that strikes the face and mouth is determined outside of this model. However, the droplet model is used to determine how much spread has occurred in the stream. This is done by modeling the location of the points where the droplets strike the face. The location of the impact in the yz plane gives a measure of the spread of the stream at the face. These locations were determined for 100 droplets and the area of the impacts was measured. This analysis indicated that the impact area of the PAVA Stream will become larger than the eye within 2 m and larger than the area of an open mouth by 3 m. This spread reduces the maximum volume of the stream that hits the eye and mouth at these distances.

Cone

As discussed in the exposure section, the cone sprays and streams are intended to affect the eye and thus produce droplets that are greater than 100 μm in size. Such droplets, while too large to inhale, could, in theory, produce respirable aerosols when they impact the face. Marshall and Knight (2000) conducted a study to determine the size of the PAVA spray droplets after impact for the two PAVA products. As discussed in the risk characterization section of this report, the study has a number of limitations. However, the study's finding that very few droplets were generated by the impact with a solid object (at 1 m) appears to be strong evidence that respirable aerosols are not formed by splatter from impact.

There is evidence that respirable aerosols are not formed by splatter from impact of a stream. Support for this finding comes from studies of inhalation of aerosols formed during showering. Studies of the size distribution and the resulting doses from the inhalation of aerosols in the shower suggest that splatter after impact is not a significant route of exposure (Finley et al., 1996; Xu & Weisel, 2003). Based on these findings, inhalation of droplets formed during impact of large droplets was not modeled.

[9] This time is actually slight before the time of impact but since the time steps are very small, the error introduced from this is not significant.

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Appendix H - Modeling Foggers

Foggers are the third type of OC sprays that are commercially available. These sprays produce a wide spray of small droplets in the range of 1-50 μm. A fogger creates a cloud of fine droplets that will cover a larger area. Because of the size of the droplets, the primary target for the OC foggers is the respiratory tract rather than the eye. Modeling exposure to a fogger used indoors requires consideration of a number of processes, including removal mechanisms and changes in the size of the droplets[10]. Once released into the cell, droplets will eventually be removed from the cell air by one of four processes. These are:

- Removal by the ventilation system or leakage around the cell door;
- Settling to the floor;
- Adhesion to the wall or ceiling; or
- Inhalation by the individual.

The last two processes are believed to remove a very small proportion of the droplets, based on the following rationale. Foggers are designed to generate droplets in the size range of 0.5 - 50 μm. Droplets this small do not contact solid objects, but flow around them with air currents. As a result, they may settle out to the floor but they do not come into contact with walls or ceilings. The volume of air inhaled by an individual is a small fraction of the total volume of air in a cell, and the removal by this route has a minimal effect on the fate of an aerosol droplet. The remaining two processes, settling and ventilation, need to be addressed.

The rate of settling is determined by the size of the droplet. Because of their small size and the time they remain airborne; droplets in foggers lose their solvent and shrink in size. As the droplets shrink, their settling rate decreases.

The approach used to model this scenario is to model the individual droplets in the room over time. This approach allows the model to determine the joint effects of removal and evaporation. The result of this modeling is a determination of the composition of the aerosol in the room over time. This composition includes the number of droplets in a given volume of air and the distribution of the size of the droplets.

Modeling Design

The model design was built around 1,200 time steps of one second duration (totaling 20 min). At the beginning of each time step the model determined the size of the droplet by sampling from the distribution of droplet sizes. Based on that the initial size of the droplet, the model determines:

1. The probability that the droplet would be removed by settling.

[10] Droplets can also coalesce to form larger droplets that would have higher settling rates. Droplets in this size range; however, tend to move with the bulk transport of air. Because of this the number of collisions between droplets of this size is small and the formation of larger droplets is not expected to be a significant factor.

2. The probability of removal by ventilation.
3. The size of the droplet at the beginning of the next time step.

Based on this data the model uses a simple binomial function to determine the removal where the probability of removal is equal to the sum of the probabilities of removal by ventilation and settling. If the droplet is removed, the model stops tracking the droplet. If the droplet is not removed, the diameter is changed and the process is repeated for the next time step. Once the droplet is removed or when the final time step occurs, the process repeats itself with another droplet. In this assessment, a total of 10,000 droplets are modeled. The time histories of the 10,000 droplets in the air create a history of the aerosol in the room. The status of the 10,000 droplets at various points in time describes how many droplets are remaining and what their sizes are.

Modeling the Settling of Aerosols

The major source of removal is by settling out of the air on to horizontal surfaces. The settling rate of a droplet is a function of the droplets' cross sectional area. Table H-1 presents the settling velocities of aerosols of different sizes based on the Heinsohn algorithm for determining the settling velocity of unit density spheres as a function of aerosol diameter (Heinsohn, 1991).

Table H-1. Droplet size (diameter) and settling velocities.

Droplet Size (μm)	Velocity (cm/s)
1	0.0034
2	0.013
3	0.028
4	0.049
5	0.076
6	0.11
7	0.15
8	0.19
9	0.24
10	0.30
11	0.36
15	0.67
25	1.8
35	3.6
45	5.8
60	10
80	17
100	25

The modeling of removal of droplets due to settling assumes that the droplets in the room are being continuously mixed as the result of random air currents associated with movement of the individual inside the room or due to thermal gradients. As a result, the model does not define the location of the aerosol in the room.

The probability that a droplet is removed by settling to the floor is based on the size of the droplet at the prior time step. The model does not determine the exact location of the aerosol; however, if the droplet is close to the floor (within k cm of the floor) it is assumed to be removed by settling. The value of k is determined based on the length of the time step in the simulation model (one second) times the settling rate of the droplet.

k = Time Step (s) * Settling Rate (cm/s) (1)

Thus if a droplet is 15 μm in size at the beginning of the prior time step then the settling rate of the droplet is 0.669 cm/s and the value of k is 0.669 cm. If the aerosol can be anywhere in a room then the probability of being within 0.669 cm of the floor is given by:

P (Height<0.669 cm) = 0.669 cm/ RH (cm) (2)

Where RH is the height of the room.

Thus, if the room is 2.4 m in height, the probability of being removed in the prior time step of one second is:

= 0.669 cm/(2.4 m * 100 cm/m)

= 0.0026

Thus for this size droplet there are 2.6 chances out of 1000 that the droplet will be removed in a one-second time period. The model tracks a droplet over each time step and uses a binomial function to determine if the droplet is removed where the probability of removal is given by Equation 2.

Modeling Removal of Droplets by Ventilation

The probability that the droplet is removed by general ventilation is given by the air exchange rate and is independent of the size of the droplet. The probability of being removed in a time step of one second is given by:

= AE (1/hr) / 3600 s/hr (3)

If the cell has an exchange rate of 1 exchange per hour, the probability of the droplet being removed is 1/3600 or 0.000278. As this calculation suggests,

settling is a more important removal mechanism for droplets that are 15 μm or larger in size in rooms that have air exchange rates of 1 hour^{-1}.

The model tracks a droplet over each time step and uses a binomial function to determine if the droplet is removed where the probability of removal is given by Equation 3.

Modeling Evaporation Rates

The final process that is modeled is the change in aerosol size. This process is very dependent on the composition of the fogger. The fogger used in this analysis is the Brand Z Fogger. This product is described as having an alcohol base. In this analysis, the spray is assumed to be a mixture of 50% ethanol and 50% water. The following table presents the data on ethanol used in the following calculations.

Table H-2. Physical Properties of Ethanol

Compound	VP (torr)	MW (g/mole)	BP (°C)
Ethanol	60	46.1	78

The evaporation of and shrinkage of droplets is driven by the following time-dependent variables, vapor pressure of the solvent mixture in the droplet, concentration of solvent and water in the air of the cell, and the transport dynamics of the solvent and water from the droplet. The following sections describe each of these factors.

Vapor Pressure

The vapor pressure of the solvent and water in the droplets is a function of the inherent volatility (i.e., vapor pressure) of the evaporating solvents (ethanol and water) and the time-dependent percentage of each solvent in the evaporating droplet. Raoult's Law is used as a starting point for characterizing the vapor pressure of the solvent/water mixture. This relationship is as follows:

$$VP_{solution} = (VP_{Pure})(Mole\ Fraction) \quad (4)$$

$VP_{solution}$ = the vapor pressure of the solvent above the solution (torr)
VP_{Pure} = vapor pressure of the pure solvent (torr)
Mole Fraction = fraction of the total moles in the solution that is the solvent (unitless).

Since many mixtures of water and organic solvents do not follow Raoult's law, Equation 4 was modified to include a term that describes the variation for ideal behavior of the mixture. The revised equation is:

$VP_{solution} = (VP_{Pure})(Mole\ Fraction)(\alpha)$ (5)

α = Thermodynamic activity coefficient

The thermodynamic activity coefficient is estimated using a physical-chemical model known as UNIFAC (Fredenslund et al., 1975). The method includes a lengthy procedure unsuitable for situations where a quick and simple calculation is required. To make the UNIFAC method easily accessible for quick calculations, the UNIFAC Activity Coefficient Calculator was developed (UNIFAC, 2004)[11]. UNIFAC uses molecular structure-activity relationships (SARs) and, since the thermodynamic activity coefficient is not constant but a function of concentration, it also uses the mole fraction of the various solvents in the solutions to calculate the coefficients for each. The value of α for the 50% mixture of ethanol and water is 1.2 at 25°C.

For the purpose of this analysis, the initial vapor pressure conditions of the solvent over the solvent/water solution were determined using Equation 5 above. The calculated expression of this vapor pressure was assumed to be a constant during the entire evaporation process. That is, this vapor pressure was used to calculate the rate of volatility for the entire solvent/water solution until all of this solution was evaporated and only nonvolatile OC active remained. This approximation will under-predict the rate early in the process when both solvent and water are evaporating and over-predict the rate when the solvent is gone and only water remains.

In addition to simplifying a complex estimation technique, the approximation appears to be appropriate since the rate of the evaporation of pure water results in a time-to-dryness that is within a factor of 2-4 of the time predicted from this rate.

Back Pressure

The second factor in evaporation is the back pressure that occurs from solvent in the air of the cell. Concentration of solvent vapors around the evaporating droplets is a function of amount of OC spray and effective air volume containing the spray. It is a well-known phenomenon that having a concentration of the same solvent in the receiving air space retards evaporation of a solvent. This so-called backpressure effect is directly proportional to the ratio of the airborne concentration to the saturation concentration for that compound over that solution. The effect is essentially nil at low concentrations but the evaporation rate becomes essentially zero when the concentration in the air over the solution is saturated.

[11] The calculator is a 32-bit Windows 95 or Windows NT application that applies a user-friendly interface to the UNIFAC method. The system's chemical species are chosen from pull-down lists. The chemical component database is fully customizable, and allows for the creation and editing of species using the UNIFAC subgroup definitions.

This model assumes that the saturation concentration for the solvent is equal to a constant equilibrium concentration derived from the vapor pressure ($VP_{solution}$) for the solvent in water calculated using the equation below:

$$C_{SAT} = \frac{VP_{solution}}{760}(1,000,000) \quad (6)$$

C_{SAT} = saturation concentration in ppm v/v.

The evaporation rate is proportioned by the ratio of the predicted airborne concentration above the droplet and C_{SAT} as follows:

$$EvapRate = (EvapRate_{MAX})(1 - \frac{CONC}{C_{SAT}}) \quad (7)$$

EvapRate = rate of evaporation (g/sec)
EvapRate $_{MAX}$ = maximum rate of evaporation (i.e., no back pressure) (g/sec)
CONC = concentration of solvent in air over evaporating droplet (mg/m^3)
C_{SAT} = saturation concentration from Equation 6 converted to unit of mg/m^3

The simplifying assumption of a constant C_{SAT} for the droplet solution appears reasonable considering that $EvapRate_{MAX}$ is driven by $VP_{solution}$. Since both $VP_{solution}$ and C_{SAT} are decreasing during evaporation of the solution, the ratio of $VP_{solution}/C_{SAT}$ should remain relatively constant as the solvent leaves the solution. In addition, as mentioned above running pure water with OC active does not change the predicted time to dryness for typical OC spray by more than a factor of 2 to 4.

Dynamics of Air Movement across the Droplet

The evaporation rate of a liquid is dependent on the relative movement of air over the liquid's surface and the distance or "fetch" of that movement. These factors and the total surface area of the evaporating droplets provide the input to the evaporation algorithm presented below.

Specifically, the evaporative source term algorithms from the 1991 EPA Engineering Manual (U.S. EPA, 1991) were used. The key equations in this document for emission from vaporizing pools are presented below along with their designations within this reference:

$$G = \frac{13.3792\ M\ P^{\bullet}\ A}{T} \left(\frac{D_{ab} V_z}{\Delta Z} \right)^{0.5} \quad (8)$$

where: G = Generation rate, lb/hr
M = Molecular weight, lb/lb mole

$P^{\cdot}$ = Vapor Pressure, in Hg
A = Area, ft^2
D_{ab} = Diffusion coefficient, ft^2/sec of a through b (in this case b is air)
V_z = Air velocity, ft/min
T = Temperature, ºK
Δz = Pool length along flow direction, ft

Gas diffusivities of volatile compounds in air are available for several existing chemicals. However, the diffusion coefficient often will not be known. An equation to estimate diffusion coefficient is expressed as:

$$D_{ab} = \frac{4.09\,x10^{-5}(T)^{1.9}\left(\frac{1}{29}+\frac{1}{M}\right)^{0.5}(M)^{-0.33}}{P_t} \qquad (9)$$

where: D_{ab} = Diffusion coefficient, cm^2/sec
T = Temperature
M = Molecular weight, lb/lb mole
P_t = Pressure, atm

Substituting:

$$G = \frac{2.79\,x10^{-3}\,M^{0.835}\,P^{\bullet}\left(\frac{1}{29}+\frac{1}{M}\right)^{0.25}\left(V_z\right)^{0.5}\,A}{T^{0.05}\Delta z^{0.5}P_t^{0.5}} \qquad (10)$$

where: G = Generation rate, lb/hr
M = Molecular weight, lb/lb mole
$P^{\cdot}$ = Vapor Pressure, in. Hg
V_z = Air velocity, ft/min
A = Area, ft^2
T = Temperature, ºK
Δz = Pool length along flow direction, ft
Pt = Overall pressure, atm

We used an iterative calculation $VP_{solution}$ for the vapor pressure of the solvent at 25ºC (T = 25+273) with molecular weight (M) and 300 ft/min (ca. 1-2 m/sec) as the relative air velocity (Vz) in the model[12]. Δz was estimated to be the square root of A which was the total surface area of all the droplets in the spray

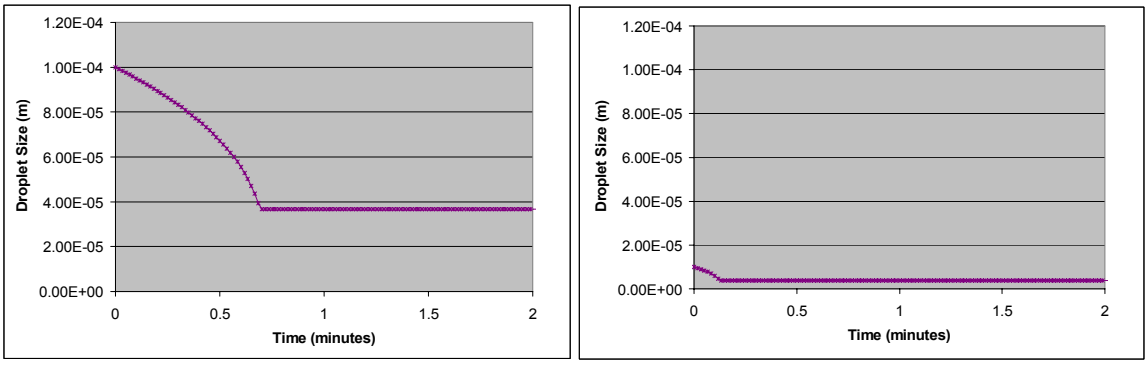
[12] This rate is higher than the settling rate for droplets below 25 μm. This may result in a slight overestimation of the rate of evaporation.

shot which was assumed to have a weight of 10 g. The overall system pressure was estimated as 1 atm.

These values and algorithms with the above assumptions were used in a standard spreadsheet to estimate the critical parameters in this analysis. Critical outputs include the airborne concentration of solvent in the effected volume of the spray from evaporation and the shrinkage of the droplets as a function of their starting diameter and time.

Figures H-1 and H-2 present the rates of change in size for the 100 μm and 10 μm droplets. As the figure indicates, the solvent and water in the smaller droplets evaporate within six seconds while the larger droplets take more than 30 seconds.

Figures H-1 and H-2. Rate of shrinkage in droplets of different sizes.



Use of Evaporation Results in the Model

The above equations were used to derive the rate of change in diameter in the one second time step. For droplets containing an initial mixture of 50% water and 50% ethanol this was found to be conservatively estimated by a 1 μm decrease in diameter per second[13]. This rate of change in diameter was used to update the diameter of a droplet at the end of each time step. The diameter was decreased in each time step until the droplet reached its terminal diameter (the final diameter of the aerosol composed of the capsaicinoids and inert solids after all of the solvents had been lost).

[13] It is interesting to note that while the fraction of ethanol in the droplet decreases over time leading to an enrichment of fraction of water in the droplet (and thus a lowering of the volatility of the mixture), the rate of change in the diameter increases as the droplet shrinks in size. This occurs because the ratio of the surface area (and thus evaporation rate) to total volume increases as the droplet shrinks.

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Appendix I - Estimating the Dietary Intake of Capsaicinoids from the Consumption of Chili Peppers and Foods Containing Chili Peppers

Individuals in the U.S. and other countries include chili peppers as part of their regular diet. This practice results in oral intake of large amounts of capsaicinoids. In this appendix, the daily doses of capsaicinoids are determined using a software program, LifeLine Version 3.0 (LLG, 2005). LifeLine Version 3.0 is currently used by the USEPA to model dietary exposures to substances in food. The program is based on the results of a national dietary survey (BARC, 2004) that records the dietary intake of individuals. The software allows the user to enter data on the level of a substance in the agricultural commodities that are used in various types of food. The software then track the foods made with the commodities and the amount of the foods consumed by individuals on a given day.

To model daily intake of capsaicinoids, the following steps were taken.

1. Using the Food Residue Translator module of LifeLine, a default distribution of capsaicinoids was applied to all peppers other than bell peppers and peppers used in baby foods.
2. This distribution of capsaicinoid residues in these peppers was a uniform distribution between 0.1 and 0.9% capsaicinoids. This distribution was selected based on the report that capsaicinoids make up 0.1 to 1% of chili peppers by weight (Rumsfield & West, 1991;Monsereenusorn et al., 1982).
3. The distribution of capsaicinoid residues in various foods was calculated. These values reflected both the distribution of capsaicinoid residues in the peppers and the amount of pepper used in each food.
4. The foods were individually reviewed and a determination was made as to whether the food was likely to use chili peppers or some other variety of sweet peppers (other than bell peppers).
5. This determination was based on the following criteria:
    a. If the food indicated that it was “Thai,” “Mexican,” “Caribbean,” or a food known to be “hot” (General Tso’s Chicken) the residue was retained.
    b. If the food was one that traditionally did not include a “hot flavor” the residue in that food were set to zero. Examples of such foods include “tuna salad,” “sausage cooked with peppers,” and “potato salad.”
    c. If the food indicated that it was “hot” such as “hot pepper sauce” the level of capsaicinoids was set at 0.9%.
6. Using this data set of dietary residues, a simulation of capsaicinoid intake was performed.

The results of the analysis are given in the following figures. Figure I-1 shows the variation of average daily intake with age. This intake includes all individuals, both consumer and non-consumer of chili peppers. The figure indicates that capsaicinoid intake increases with age and for adults is in the range of 0.12- 0.14

mg/kg or 8-10 mg per day. These findings appear to be reasonable since adults consume foods that are more piquant than the foods consumed by children. The distribution of doses of capsaicinoids in adults during the summer (when intakes are highest) is given in Figure I-2. The figure indicates that on any given day the majority of individuals do not consume foods consuming capsaicinoids. However, approximately 15% of the population consumes at least one food containing capsaicinoids. In this 15% of the population, the doses range from <0.1 mg/kg to more than 10 mg/kg (or <7 to 700 mg) of capsaicinoids per day.

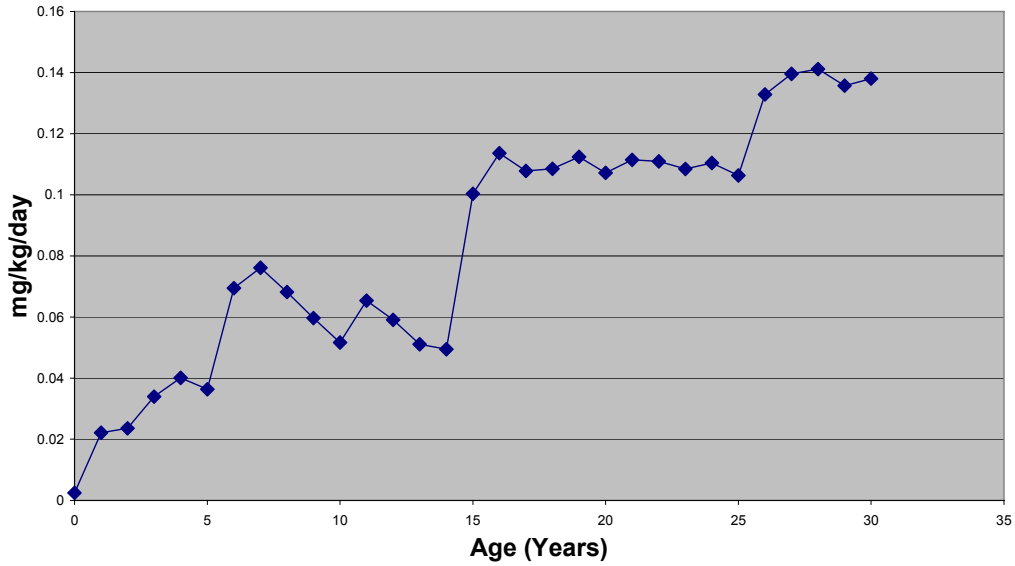

Figure I-1. Average intake of capsaicinoids by age in the US Population.

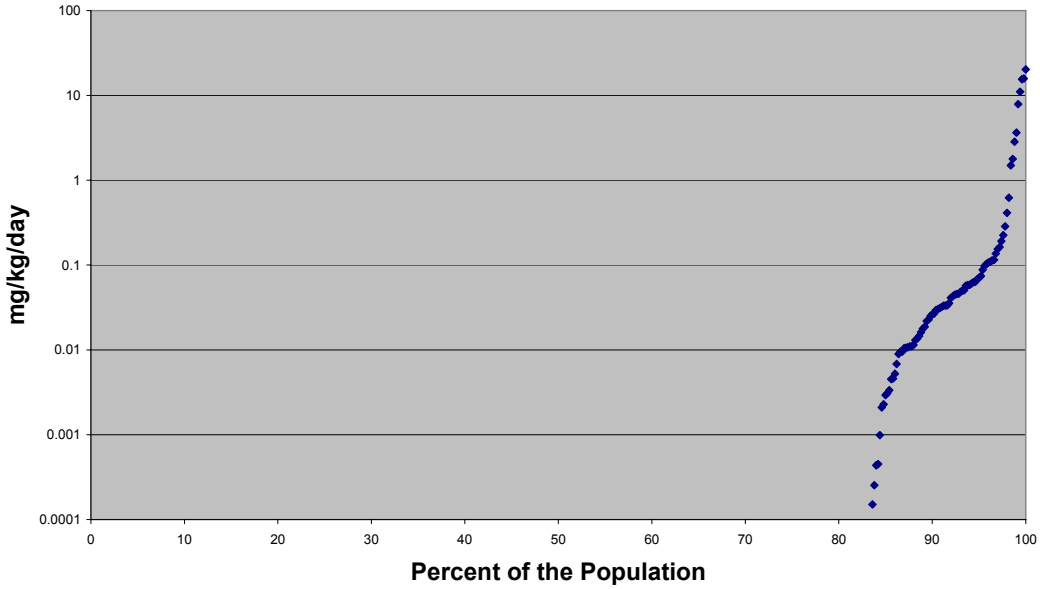

Figure I-2. Distribution of Daily Intakes of Capsaicinoids in the U.S. Population.

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Appendix J – Other Sources for Operational and Toxicological information on Nonivamide (PAVA)

For more information on PAVA use in the UK, the authors would like to refer the reader to: "Comparison of CS and PAVA: Operational and Toxicological Aspects 88-04," by Graham Smith, Martin Macfarlane and Jasmin Crockett, Home Office Scientific Development Branch (HOSDB) at http://scienceandresearch.homeoffice.gov.uk/hosdb/publications/police-weaponry/Compairson_CS_and_PAVA?view=Standard&pubID=385487

For more information on chemical incapacitant use and training procedures in the UK, the authors would like to refer the reader to: Association of Chief Police Officer of England, Wales & Northern Ireland, "Guidance on the Use of Incapacitant Spray", September 19, 2006 at http://www.acpo.police.uk/asp/policies/Data/guide_use_incapacitant_spray_website_updated_sept06_11x10x06.doc

For more information on a toxicological review of PAVA done in the UK by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (non-food) (COT), the authors would like to refer the reader to: "COT report on PAVA, COT statement on the use of PAVA (nonivamide) as an incapacitant spray (COT/04/6 - November 2004)" at: http://www.advisorybodies.doh.gov.uk/cotnonfood/pava04.htm AND its predecessor, "COT statement on the use of PAVA (nonivamide) as an incapacitant spray (COT/02/2 - April 2002)" at http://www.advisorybodies.doh.gov.uk/cotnonfood/pava.htm