Response to Federal Register Comments for DMF

Claudia M. Troxel
Nancy Kim

Summary of proposed AEGL values for DMF					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	160	110	90	55	38
AEGL-3	320	220	180	110	76

AEGL-1: Not recommended

AEGL-2: AEGL-3 ÷ 2 (because NAC felt the AEGL-3 values were protective base on monkey data)

AEGL-3: No mortality in rats exposed to 3700 ppm for 3 hours (Macdonald, 1982). Possible that proposed values are conservative. No effects observed in monkeys exposed to 500 ppm for 6 h/d, 5 d/wk for 2 or 13 wk, and rats exposed to 400 or 800 ppm DMF for 6 h/d, 5 d/wk for 13 wk exhibited only minimal to moderate necrosis of individual hepatocytes. Rats exposed to 200 ppm did not show evidence of any liver injury.

Total UF of 30

3 for interspecies: appears there are limited species differences regarding toxic response to DMF. Similar hepatic effects in humans as in animals. The mechanism of hepatotoxicity related to metabolism by CYP2E1 to reactive metabolite. Study demonstrates similar K_m and V_{max} between rat and human liver

10 for intraspecies:

- CYP2E1 can be induced by alcohol, diabetes, and obesity
- Prior consumption of alcohol can exacerbate DMF toxicity
- Detoxification is partly dependent of glutathione conjugation; if GSH depleted, increased exposure to reactive metabolite
- DMF exposure can result in hepatotoxicity, so those with compromised liver function at increased risk

Time scaling:

Default value of n should be used in the temporal scaling of AEGL values across time. However, if one applies the default value of n = 1 for extrapolating from shorter to longer exposure periods, one obtains a 4 h value of 93 ppm and an 8 h value of 46 ppm. Using a default value results in AEGL values that are inconsistent with the available human data. Humans were exposed by inhalation to 87 ppm DMF for 4 h in a study designed to assess the metabolism of DMF (Kimmerle and Eben, 1975b). Although the study was not designed to assess the toxic effects resulting from DMF exposure, whatever effects may have been encountered were clearly not severe enough to be classified as AEGL-3 endpoints. Therefore, in the absence of any further data, an n of 2 was selected as a reasonable compromise between the possible values for n as reported by ten Berge et al. (1986).

AEGL-3 values are therefore derived using an n=3 for extrapolation to 10 and 30 min and 1 h, and an n=2 for extrapolation to 4 or 8 h.

Comments received from E.I. duPont Nemours, Inc., a producer of DMF

Overall, they think the numbers are too conservative, and that the AEGL values do not agree with the body of data on DMF.

- The 4-hour AEGL-2 is 55 ppm, while individuals were exposed to 87 ppm for 4 hours in a metabolism study.
- Data on repeated-exposure studies documented that no deaths occurred in monkeys exposed to 500 ppm or rats exposed to [800] ppm for 13 weeks, but the 10-minute AEGL-3 is 320 ppm.

Generally, NAC agrees with the comments from duPont, as there is already a statement in the AEGL-3 derivation section to that effect. However, there do not seem to be any viable alternatives at this point.

COMMENTS ON EPICHLOROHYDRIN TECHNICAL SUPPORT DOCUMENT

Derivation of AEGL-1 values.
The odor threshold should not be used as support. The values come from a secondary source. The cited values are in such a broad range (.08-12 ppm) as to be meaningless without a carefully controlled experiment with comparison to standards. If any good data exist, they should be applied to determination of an LOA, not the AEGL-1.

Is the Enterline reference a secondary source? If so it is not an appropriate basis for a derivation.

Response: AEGL-1 derivation needs to be revised because we no longer base AEGL-1 values on odor detection. Two proposals are presented for AEGL-1.

Proposal No.1: Use the UCC (1983) report that showed pharyngeal irritation in one of four subjects exposed to 68 ppm epichlorohydrin for 2 minutes. Exposure to 136 ppm resulted in irritation to the eyes and pharynx in two of four subjects.

Applying an uncertainty factor of 3 to the POD of 68 ppm and scaling based on n = 0.87 results in an AEGL-1 value for 10 minutes = **3.6 ppm**. This value should be maintained across all exposure durations. This chemical is an irritant.

Proposal No. 2: The NAC/AEGL Committee could recommend no AEGL-1 values because they would be below the level of odor detection. Shell Oil (1992) noted that epichlorohydrin is not detectable below about 10 ppm (OT_{50} according to Shell Oil). There is no evidence of irritation occurring at $\leq$10 ppm. Therefore, any values derived would below the odor detection level as shown by the results in Proposal No. 1 above.

Calculation of LOA for Epichlorohydrin (see next page for derivation)
The LOA = **46 ppm**

Derivation of the Level of Distinct Odor Awareness (LOA) for Epichlorohydrin

Derivation of the Level of Distinct Odor Awareness (LOA)

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than one-half of the exposed population will experience at least a distinct odor intensity and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al., (2002).

The odor detection threshold (OT_{50}) for epichlorohydrin is calculated from the odor threshold of 10 ppm (50% of unconditioned personnel) reported by Shell Oil (1992) and adjusted by Van Doorn (2002):

10 ppm × 40 ppm/100 ppm = 4.0 ppm

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$$I = k_w \times \log(C/OT_{50}) + 0.5$$

For the Fechner coefficient, the default $k_w = 2.33$ will be used because of the lack of chemical specific data.:

$3 = 2.33 \times \log (C/4.0) + 0.5$, which can be rearranged to
$\log (C/4.0) = (3 - 0.5)/2.33 = 1.07$, and results in
$C = (10^{1.07}) \times 4.0 = 34.4$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day live factors, such as sex, age, sleep, smoking, upper airway infections, and allergy, as well as, distraction increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds), which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustments for distraction and peak exposure lead to a correction factor of 4/3 = 1.33.

LOA = C × 1.33 = 34.4 ppm × 1.33 =46 ppm (van Doorn et al., 2002)

Therefore, the LOA for ethylene oxide is **46 ppm**.

ATTACHMENT 8

Nitrogen Dioxide

Response to Federal Register Comments of October 7, 2004

One comment was received in response to the Federal Register notice for AEGL values for nitrogen dioxide. This comment was from Dr. George Alexeef regarding AEGL-1 values. Dr. Alexeef has requested that the NAC reconsider AEGL-1 values because effects were described at the concentration used as the basis for AEGL-1.

AEGL-1 values for nitrogen dioxide were set at 0.5 ppm for all time points. The basis for AEGL-1 was a study by Kerr et al. (1979, 1978) in which asthmatics were exposed to 0.5 ppm for 2 hours with exercise. At this concentration the odor was perceptible but the subjects became unaware of it after about 15 minutes. Seven of 13 asthmatics reported symptoms with exposure including two with slight burning of the eyes, one with a slight headache, three with chest tightness, and one with labored breathing during exercise. No changes in any pulmonary function tests were found immediately following the chamber exposure.

The NAC considered 0.5 ppm a NOAEL for objective tests of pulmonary function in **exercising asthmatics**. Dr. Alexeef considers the subjective symptoms an effect level. This issue was discussed by the NAC prior to voting overwhelmingly to adopt the AEGL-1 values. Neither new data nor alternatives to the standing NAC decision have been offered. Therefore, in the absence of specific recommendations or new information the NAC has no reason to reconsider AEGL-1 values for nitrogen dioxide. The values, as adopted, were based on the best data available and discussed openly by the full committee.

For comparison, the National Ambient Air Quality Standard is 0.053 ppm (annual average) with Significant Harm Levels of 2 ppm for a 1-hour average and 0.5 ppm for a 24-hour average; the Level of Concern (10% of the IDLH value) is 5 ppm[1]. The state of California has adopted 0.25 ppm as the standard for a 1-hour exposure to protect sensitive individuals.

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[1]The 5 ppm value for the Level of Concern was established prior to revision of the IDLH value from 50 ppm to 20 ppm in 1995.

ATTACHMENT 9

October 6, 2004

Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPTS)
EPA
1200 Pennsylvania Avenue
Washington, DC 20460-0001

Docket control # OPPT-2004-0079 Peracetic Acid AEGL-2 values

I would like to state my concern regarding the explanation in the Peracetic Acid TSD of the exposure time periods that are associated with symptoms reported by investigators. Table 2 in the TSD accurately reports Fraser's exposures and the investigator's health effects. The question is how to interpret the time notations: is this an exposure 'for' or 'at' any stated time. This is a fogging simulation with the generation of peracetic acid exposure by a unit turned on at time 0 and then off after 5 minutes of generating the "fog" with exposures and investigator symptoms reported for 45 minutes. Rather than an exposure of "3.12 to 4.67 mg/m3 for 15 to 20 minutes" as reported in 5.1, Table 2 shows this exposure existed from 15 to 20 minutes after fogging began, a 5 minute period. Section 6.3 goes further by eliminating the lower end of this range and states that " a slightly lower concentration of 4.67 mg/m3 ..for exposure durations up to 20 minutes". Further the more serious health effects are omitted in Section 6.3. where 3.5 minutes exposure to 15.6 mg/m3 is reported to cause "lacrimation" while Table 2 states there was "extreme discomfort".

Although McDonagh conducted a study in a plant for up to 3 hours, it is unclear in the TSD summary what the exposure level was during the whole time period. Rather as in Fraser, there likely was variable exposure over the 3 hours in an industrial operation. According to section 2.2 the .53 mg/m3 exposure was for a 10 minute sample while 5.1 states this level existed for "up to 3 hours". The investigators also state that "the background level of peracetic acid was fluctuated significantly". Basically the exposures and associated symptoms in both studies are for short time periods leaving an open question what the resulting health effects would be for longer time periods, especially 1, 4 and 8 hours

In addition, the two reports (Fraser and McDonagh) relied on are not per reviewed studies and the subjects are few with no systematic interview. Although internal industrial hygiene company reports can often be used by the AEGL committee, there are significant questions if these reports do not include the practices normally found in a human exposure study, namely the systematic investigation of health effects that can be matched with exposure periods of known duration. In both studies the health effects reported are by an unknown number of investigators in Fraser and two investigators in McDonagh, not neutral or unbiased subjects. The subjects were not blind to the exposure levels and there are few subjects with little power to generalize to larger populations. For example, although Fraser reported extreme discomfort at 2 ppm after 5 minutes of exposure, it is unknown if there were more subjects, some might experience this effect at lower values or that some subjects might experience more serious symptoms.

Please note that section 2.6 should be labeled section 2.3. I urge the committee to lower the AEGL-2 values by time scaling for all values greater than 10 minutes. Although the resulting levels will probably be lower that the AEGL 1 values at longer time periods, the evidence is not available to state with certainty that these effects would not occur at 4 or 8 hours. Since the matched health effects, exposure levels and exposure periods in both studies used for AEGL 1 values are for short time periods, and few animal studies for extended time periods, the committee should consider lowering the AEGL 1 values for the longer time periods if they approach or exceed the AEGL 2 levels.

Response: I am not sure of issue being raised in this comment. Controlled human studies are not always available for deriving AEGL-values. However, it is my understanding that we use the available human data wherever possible. The AEGL-1 values are below any concentration shown to cause irritation and should be protective of the general public.

Sincerely,

John S. Morawetz

c: Larry Gregoire
Eric Bray
Michael Sprinker
Bill Kojola, AFL-CIO
George Rusch, AEGL Chairman
Paul Tobin, EPA

3725 Andrew Ave.
Cincinnati, OH 45203
October 1,2004

Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPTS)
Environmental Protection Agency
1200 Pennsylvania Avenue
Washington, DC 20460-0001

Docket control # OPPT-2004-0079 Proposed AEGLs for Peracetic acid

I write to seek clarity on a few points in the Technical Support document which you have written on peracetic acid, and specifically how you have made use of Fraser and Thorbison (1986) to estimate concentrations and the related acute health effects.

I have been looking through both documents and remain unclear about the concentration d t s used. In particular, you report that 15.6 milligrams per cubic meter of peracetic acid is equivalent to 5 ppm (on pg 5 line 14) - but I don't believe that 5 ppm of peracetic acid is necessarily equivalent to 5 ppm "Total as H_20_2)), the units used in Fraser and Thorbison (1986). Your document seems to be making that assumption since you are using 6.2 mg/m^3 peracetic acid to correspond to Fraser's use of 2 ppm as H_20_2 - for ex on pg 19 of your TSD.

Response: The rationale for converting ppm as H_2O_2 to mg/m^3 of peracetic is that one mole H_2O_2 is equivalent to one mole peracetic. Therefore, ppm of H_2O_2 can be converted to mg/m^3 peracetic acid.

Also, your discussion in section 6.3 (pg 19 line 20) may not clearly summarize the data in Tables 1 and 2 of Fraser. You say that exposure to 2 ppm "for 2 minutes was also considered tolerable"; but this seems to be a very selective reading of the last line of Fraser's Table 1, which is fairly confusing in that it presents variability due to location and time in the same table. Both tables together (including Table 2) could also be read to mean that this same concentration caused unbearable irritation (Table 1 middle) or extreme discomfort (Table 2 top) over brief periods of exposure.

Response: This uncertainty regarding the effects at 2 ppm was taken into account when a lower concentration (1.5 ppm) was used as the point of departure for AEGL-2. Table 2 in the document and Fraser and Thorbinson's table showed fairly consistent responses at exposure concentrations ≤1.5 ppm (4.7 mg/m^3).

One difficulty in interpreting Fraser is estimating what the short-term average exposures might have been over the first 2,5 and 10 minutes of their fogging study, since the exposure seems to have 'ramped up quickly to (above?) 5 ppm in the first 3 minutes and

then gradually declined through 2 ppm at about 5 minutes. To come up with estimated short-term averages from this incomplete data seems to me to require some estimates of area under a plausible curve (then divided by duration), which it appears that you have not done.

It may be the case that your uncertainty factor of 3 takes care of these problems in the derivation of the proposed AEGL-2, but I believe additional attention to these issues is necessary before moving forward with the process.

Response: All studies of this type are accompanied by varying degrees of uncertainty. The exposure concentrations and effects presented by Fraser and Thorbinson were difficult to interpret. It may be possible to calculate the area-under-the-curve; however, this value is likely to be higher than that the point of departure reported in the document. Therefore, we have taken the more conservative approach. The uncertainty factor of 3 does provide an added level of protection.

Sincerely,
Thurman B. Wenzl ScD CIH
Adjunct Associate Professor
University of Cincinnati

Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPT)
EPA
1200 Pennsylvania Avenue
Washington, DC 20460-0001

October 6, 2004

Docket control # OPPT-2004-0079 Trichloroethylene values

I would like to raise concerns regarding the 10 and 30 minute AEGL-3 values recommended by the AEGL Committee for Trichloroethylene (TCE). The setting of environmental exposures above the anesthetic level, an AEGL-3 of 10,000 ppm for 10 minutes, would be potentially life threatening. The question is: If trichloroethylene was used safely as an anesthetic in an operating room, is it therefore safe for an environmental release? If the committee was setting safe levels for hospital use of TCE, the committee's values may stand. But this is neither the population nor the context of the AEGL's intended use.

Although there is evidence that TCE it is not immediately lethal to patients prepared for surgery, my concerns is that exposures to the general public without the medical support available in an operating room could be life threatening, the other AEGL-3 definition besides immediate lethality. The general population will not have medical support readily available. It is potentially dangerous to take safety data from the operating room and assume that it is transferable to the general public. Even healthy individuals who have just consumed a meal are at significant risk of aspiration of vomit and likely death. This danger is will recognized and leads to prohibitions from eating before surgery.

In hospitals, exposures at anesthetic levels occur to people who have been medically screened to be fit for an operation, they are monitored closely during the operation, the level of anesthetic dose is adjusted to provide a margin of safety, and they recover in a controlled hospital environment where they are regularly monitored by medical staff. What is "safe" under these conditions is not the same as during community exposures. People with pre-existing medical problems, such as cardiovascular disease, may be more susceptible to the lethal effects of these agents, there will be no trained medical staff observing for complications or reducing the exposure if problems do occur, and recovery from exposure likely will occur in an uncontrolled environment remote from expert care.

Section 7.3 on the derivation of AEGL-3 states that "the obtained values are considered to be too low compared to the available human evidence". The studies that support this statement must be cited. The studies cited in the Technical Support document are mostly to exposures at 200 ppm or less. One study exposed people to 1,000 ppm for 2 hours but subjects began feeling lightheadedness, lethargy or dizziness, supportive of lower values.

The bottom line is that the one hour value of 3,800 ppm (.38%) should be used for the 10 and 30 minute values to provide a margin of safety for the threshold of potentially life threatening anesthetic effects. This value is consistent with the threshold of anesthesia found in the studies of Pembleton, 1974, Parfitt, 1999 and Langton-Hewer, 1975.

Sincerely,

John S. Morawetz

c: Larry Gregoire
Secretary Treasurer's Office
Eric Bray
Michael Sprinker
Bill Kojola, AFL-CIO
George Rusch, AEGL Chairman
Frank Mirer, UAW

Response to COT's Comments for PMM

Claudia M. Troxel
Susan Ripple

Properties:

- Oily yellow liquid
- Unbearable acrid odor
- Irritant, lacrimator

Human data:

- ***Lethal effects:*** case report of exposure to unknown concentration of vapor and liquid resulting in massive hemorrhaging lung edema with simultaneous heart, circulatory, and kidney failure from resultant hypoxia

- ***Nonlethal effects:*** Odor threshold (secondary sources)
  0.001 ppm (Ruth); 0.24 ppm (Russian)

LETHAL ANIMAL DATA (only rats)

***Vernot et al.*, 1977**; 1-hr LC_{50}

11 ppm (males);

16 ppm (females);

13.5 ppm (combined)

Stauffer Chemical Co., 1971; [nominal or measured conc. ?]

13 ppm (combined); 1-hr LC_{50}

9 ppm no deaths; 18 ppm: 7/10 died

Eye/mucosa irritation, dyspnea, acute depression

Gage, 1970 (purity unknown; nominal conc.)

100 ppm for 1 hr – 4/4 M rats died (pulmonary edema)

10 ppm for 6 hr – 3/4 died; lethargy and respiratory difficulty

NONLETHAL ANIMAL DATA (only rats)

Knapp et al., 1987 (abstract)

15 M and Fe SD rats/group exposed to "cumulative" mean air concentrations 6 h/d, 5 d/wk, for 2 wks

Results:

- **0.02 ppm** - No effects
- **0.13 ppm** - Mild nasal epithelial changes
- **1.15 ppm** - Haircoat stains, labored breathing, tremor, ↓ bw, ↑lung wt, pulmonary edema, ↑ mucous secretions, alveolitis, interstitial fibroplasia, mild nasal epithelial changes

NONLETHAL ANIMAL DATA (only rats)

Knapp and Thomassen, 1987

18 SD rats/sex/group exposed 6 h/d, 5 d/wk, for 70 to 72 d

Results:

- **0.014 ppm** - No effects
- **0.079 ppm** - 1 M, 1 Fe had residues of purulent or serum exudate
- **0.58 ppm** - Salivation (d 18) and sneezing (d 59); ↓ bw, ↑lung wt, mucous in trachea, respiratory nasal epithelium changes, residues of purulent or serum exudate, focal subacute interstitial pneumonia

NONLETHAL ANIMAL DATA (only rats)

Gage, 1970 (purity unknown; nominal conc.; mixed with acetone)

Results

- **2 ppm** (in acetone) for twenty, 6 hr exposures; 4 M rats; initial respiratory difficulty, none died; gross necropsy - pulmonary congestion
- **0.5 ppm** (in acetone) for twenty, 6 hr exposures; 4 M and 4 Fe rats; no signs of toxicity; no gross necropsy findings

Summary of proposed AEGL values for PMM					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	0.018	0.018	0.014	0.0090	0.0060
AEGL-2	0.044	0.044	0.035	0.022	0.015
AEGL-3	0.54	0.38	0.30	0.075	0.038

AEGL-1: Rat NOAEL of 0.079 ppm for 6 hr/d, 5 d/wk for 70-72 exposure days (Knapp and Thomassen, 1987)

AEGL-2: Mild/minimal focal subacute interstitial pneumonia and ↑ lung wt in rats exposed 0.58 ppm for 6 hr/d, 5 d/wk; 70-72 d (Knapp and Thomassen, 1987)

AEGL-3: No mortality in rats exposed to 9 ppm for 1 h (Stauffer Chemical Co., 1971)

COT COMMENTS
3 Main areas of concern:

- The NAC should consider including a MF to account for the poor data quality
- Concern that AEGL-1 and -2 appear to be based on systemic endpoint of pulmonary infection following a single exposure to an irritant
- The application of uncertainty factors (adjusted composite UF instead of individual components)

AEGL-3

Although not specifically questioning derivation of AEGL-3, COT commented that TSD dismisses other published studies as inadequate for various reasons; but these arguments are not very convincing since the papers relied upon have their own limitations as well

Current AEGL-3 is based upon no-effect level for death in rats at 9 ppm for 1 hr (Stauffer, 1971). On hindsight, this POD is questionable because:

- Not stated if measured or nominal exposure conc.
- Very close to calculated LC_{50} of 13 ppm

Alternative approach: Divide the LC_{50} of 11 ppm in male rats (Vernot, 1977) by 3 - supported by the LC_{50} of 13 ppm in (Stauffer, 1971).

➢ **Therefore, POD = 11 ppm ÷ 3 = 3.7 ppm**

AEGL-3, con't

POD = 3.7 ppm

UF:

- 10 for interspecies ?
- 3 for intraspecies – mechanism of toxicity direct contact effect; death by pulmonary edema

n = default of 1; 3

➢ **NOTE:** Rats exposure to 0.58 ppm for 6 h/d, 5 d/wk, for 70 to 72 d: only effects related to repeated exposures

AEGL-3					
UF	10 min	30 min	1 hr	4 hr	8 hr
30	0.22	0.16	0.12	0.031	0.015
10	0.67	0.47	0.37	0.092	0.046

Comment:

AEGL-1 and -2 are based on the NOAEL or LOAEL for repeated exposure effects (6 hr/d, 5 d/wk for 70-72 d); mainly for prevention of pneumonia. NAC appears to be adopting the position that prevention of opportunistic pulmonary infection following a single exposure to an irritant is the proper public health end point for mercaptans and other irritants

Alternatives:

AEGL-2, could divide the AEGL-3 by 3

AEGL-1 – although from a secondary source, could use the odor threshold of 0.001 ppm (Ruth) on the basis that odor is "unbearable"

Summary of Alternative AEGLs					
AEGL	10 min	30 min	1 hr	4 hr	8 hr
Current values					
1	0.018	0.018	0.014	0.0090	0.0060
2	0.044	0.044	0.035	0.022	0.015
3	0.54	0.38	0.30	0.075	0.038
AEGL-1:odor; AEGL-2: AEGL3÷3; AEGL-3: ⅓ LC_{50}; UF 10					
1	0.001	0.001	0.001	0.001	0.001
2	0.22	0.16	0.12	0.031	0.015
3	0.67	0.47	0.37	0.092	0.046
Same as above, but UF 30					
2	0.073	0.053	0.040	0.010	0.0050
3	0.22	0.16	0.12	0.031	0.015

December 13, 2004

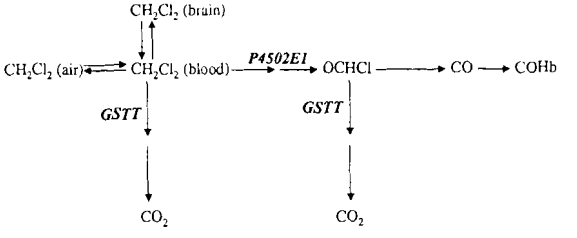
TSD Methylene chloride

Chemical Manager: B. Benson
Staff Scientist: P.M.J. Bos

Reasons for PBPK-modeling

- Two different toxicity endpoints
  - CNS-depression, related to DCM concentration in brain
  - COHb-formation, via biotransformation to CO
- Switch of toxicity endpoint between 10 min and 8 hours of exposure
  - CNS-effects occur soon after onset of exposure
  - Peak levels of COHb can be reached hours after exposure
- No data available to estimate DCM concentration in air from predetermined COHb level
- PBPK-modeling is the only way for AEGL-derivation for DCM

Metabolism scheme of DCM



Construction of the model: *Summary*

- PBPK-modeling
  - Combination of components previously peer reviewed, accepted and used for risk assessment by different organizations
    Andersen et al. (1991): COHb formation
    Reitz et al. (1997): addition of brain compartment
  - DCM concentration in brain **and** COHb formation within one model
  - Development of specific algorithms to estimate the time-concentration relation for predetermined DCM concentrations in brain and predetermined peak COHb levels (from TSD on CO)

PBPK-model: Conclusions

- Most appropriate dose metrics (target tissue concentrations) are adequately predicted within one model:
  - good reproducibility of original models
  - adequate prediction of COHb and DCM in blood in both human and rat
- Kinetics are similar in humans and rats
  - adequate prediction at high concentrations
- Model is applicable for AEGL-derivation

Conclusions

- The DCM concentration in brain **and** the COHb level can be adequately predicted within one model
- Saturation of the CO-pathway and GSTT polymorphism can be adequately accounted for
- Time extrapolation based on the appropriate dose metrics is possible with the PBPK-model
  - calculation of the DCM concentration in air from a predetermined COHb level is possible **only** with a PBPK-model
- PBPK-model is essential for the calculation of the intersection of the time-curves for the two dose metrics

Model application: *AEGL-1*

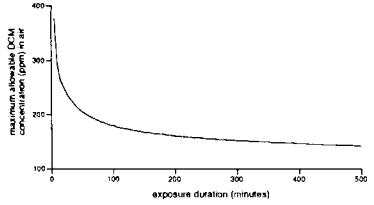
No AEGL-1 for CO

CNS-depression

- Point of departure: Stewart et al (1972)
  - 1-h exposure to 515 ppm (n=8)
    no complaints
  - ***1-h exposure to 514 ppm***, 1-h exposure to 868 ppm (n=3)
    light-headedness and altered VER during the second hour
  - 2-h exposure to 986 ppm (n=3)
    no eye, nose, or throat irritation
    light-headedness (2/3); difficulties to enunciate (1/3) after 1 h; altered VER

Model application: *AEGL-1*

- Human data: 1 hour to 514 ppm DCM
  - UF=3 ⟶ brain concentration: 0.021 mM



AEGL-1 derivation

AEGL-1 Values for methylene chloride				
10-minute	30-minute	1-hour	4-hour	8-hour
290 ppm (1024 mg/m³)	230 ppm (812 mg/m³)	200 ppm (706 mg/m³)	*160 ppm (565 mg/m³)*	*140 ppm (495 mg/m³)*

AEGL-2 derivation

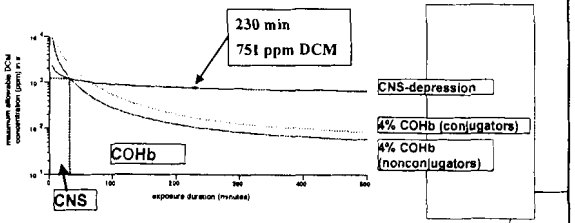
- CNS-effects
  - 230 min to 751 ppm as a conservative NOAEL *(Winneke, 1974)*
  - related to CNS concentration in the brain
- COHb-related effects
  - no data for DCM
  - compliance with TSD for carbon monoxide:
    additional COHb of 4% (based on a reduced time until onset of angina during physical exertion in patients with coronary heart disease)

AEGL-2 derivation

- CNS-effects
  - Starting point: NOAEL at 230 min exposure to 751 ppm *(Winneke, 1974)*
  - DCM concentration in brain: 0.137 mM
  - no interspecies UF
  - intraspecies UF = 1
    effects studied are sub AEGL-2 effects
    mechanism of action will not vary greatly between individuals
    intraspecies UF >1 will lead to unrealistic AEGL-2 values for CNS effects
- COHb level
  - 4% in compliance with AEGL-2 for carbon monoxide

AEGL-2 derivation

- Human data: 230 min to 751 ppm DCM
  - Dose metrics:
    brain concentration: 0.137 mM;
    4% COHb



AEGL-2 derivation

AEGL-2 Values for methylene chloride

Endpoint	10-minute	30-minute	1-hour	4-hour	8-hour
CNS-effects	1700 ppm	1200 ppm	1000 ppm	740 ppm	650 ppm
COHb (conj)	8400 ppm	2600 ppm	1100 ppm	160 ppm	85 ppm
COHb (non-conj)	4600 ppm	1400 ppm	560 ppm	100 ppm	60 ppm

AEGL-2: Human data

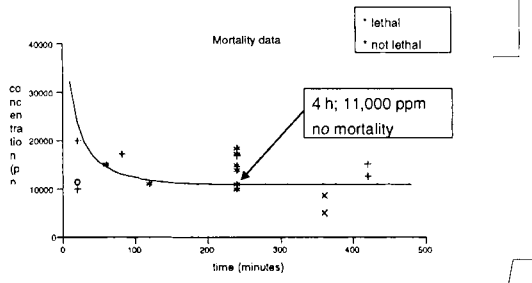
- Bicycle ergometer
  - 2 h to 500 ppm; up to 150 W
  - 1 h to 750 ppm; 50 W
- Occupational data (*Moynihan-Fradkin, 2001*)
  - 8-min TWA: 89-143 ppm; 41-969 ppm
  - 15-min TWA: 170-240 ppm; 140-1700 ppm
  - Effects reported: headaches (dermatitis, skin cracking), apparently no functional impairment

AEGL-3 derivation

- No adequate human data on mortality related to CNS-depression
- Compliance with TSD for carbon monoxide
  - no life-threatening symptoms at 40-56% COHb in healthy subjects
  - intraspecies UF of 3 used at corresponding CO concentrations
  - final AEGL-3 CO concentrations in air correspond to approximately 15% COHb

AEGL-3 derivation: *animal mortality*

- + mouse; * rat; o rabbit; x guinea pig

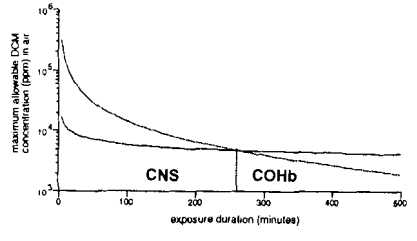


AEGL-3 derivation

- CNS-related mortality
  - starting point: 4-h exposure to 11,000 ppm in rats *(Haskell Laboratory, 1982)*
  - DCM concentration in rat brain: 3.01 mM
  - interspecies UF = 1
    - susceptibility between species is small
    - human PBPK-model is used
  - intraspecies UF = 3
    - mechanism of action (CNS-depressing effects) will not vary greatly between individuals
- COHb level
  - 15% in compliance with AEGL-3 for carbon monoxide

Model application: *AEGL-3*

- Rat data: 240 min to 11,000 ppm
  - human brain concentration: 1.0 mM



AEGL-3 derivation

AEGL-3 Values for methylene chloride					
Endpoint	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
CNS-effects	12,000 ppm	8500 ppm	6900 ppm	4900 ppm	4200 ppm
COHb (conj)	--	--	--	--	--
COHb (non-conj)	155,000 ppm	52,000 ppm	25,000 ppm	5300 ppm	2100 ppm

Summary of AEGL values

Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	290 ppm	230 ppm	200 ppm	*NR*	*NR*
AEGL-2 (Disabling)	1700 ppm	1200 ppm			
Non-conjugators			*560 ppm*	*100 ppm*	*60 ppm*
AEGL-3 (Lethal)	12,100 ppm	8500 ppm	6900 ppm	4900 ppm	
Non-conjugators					*2100 ppm*

Update on Vinyl Acetate

Claudia Troxel
Richard Thomas

The AEGL-2 was based on a rat study (Bogdanffy et al. 1987) in which exposure for 6 h to 1000 ppm caused reversible nasal lesions, with the stipulation that the pathologist be contacted to confirm this.

The report from the pathologist does indeed confirm that the lesions are reversible.

ATTACHMENT 14

December 13, 2004

TSD Chloroacetaldehyde

Chemical Manager: M. Payton
Staff Scientist: M. Draaijer / P.M.J. Bos

Chloroacetaldehyde: Uses

- Chemical intermediate in manufacturing of chemicals
- Control of growth of algae, bacteria, and fungi in water

Chloroacetaldehyde: Physical-chemical properties

- Molecular weight: 78.5
- Colorless liquid
- Water solubility: soluble
- Boiling point: 85°C (pure substance)
- Odor: acrid, penetrating
- Flammability: not flammable

Chloroacetaldehyde: Human data

- No human data available
- Statement in a report on acute toxicity (Dow 1952)
  - "Every concentration employed including the lowest (10 ppm) produced lachrymation and nasal irritation in humans within a few minutes".

Chloroacetaldehyde: Animal data

Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Guinea pig	25	7 h	0/10	Dow 1952
	50	4 h	0/10	
	100	2 h	0/10	
	400	0.5 h	7/10	
Rat	10	7 h	0/20	Dow 1952
	25	7 h	19/20	
	50	1 h	0/20	
		3.5 h	20/20	
		4 h	18/20	
	100	0.2 h	0/19	
		2 h	20/20	
	400	0.1 h	1/20	
		0.25 h	20/20	
		0.5 h	19/20	

Chloroacetaldehyde: Animal data

Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	44	1 h	0/10	TNO 1987
	159		3/10	
	203		4/10	
	243		10/10	
	309		10/10	
	596		10/10	
	2643		10/10	
	203-243	1 h	LC_{50}	

Chloroacetaldehyde: Animal data

Non-lethal toxicity

- Rat data
  - TNO 1987
  - Dow 1952
- Limited data on other species

Chloroacetaldehyde: Animal data

TABLE. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Guinea pig (n=10)	25	7 h	General observations:	Dow 1952
	50	4 h	• Dose-related eye and nasal irritation	
	100	2 h	• At the higher concentrations: labored breathing	
	400	30 min	• At some exposure levels: slight drowsiness	
Rat (n= 19 or 20)	10	7 h	General observations:	Dow 1952
	25	7 h	• Dose- and time-related eye and nasal irritation	
	50	1, 3.5, 4 h	• At the higher concentrations: labored breathing	
	100	0.2 , 2 h	• At some exposure levels: slight drowsiness	
	400	0.1, 0.25, 0.5 h		
Rat	5	7 h/d, 5 d/w, 8 exposures in 10 d	Slight nasal irritation, very slight eye irritation	Dow 1952
Mouse			Slight nasal irritation	
Guinea pig			No effects reported	

Chloroacetaldehyde: Animal data

TABLE. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat (n=10)	44 159 203 243 309 596 2643	1 h	At all concentrations: closed eyes, salivation Decreased lung function (e.g. lung edema at all concentrations, with atelectasis in some dead animals in higher exposure groups, labored breathing) At the higher doses: wet nares, nasal discharge along with wet and soiled heads and breasts	TNO 1987

Chloroacetaldehyde: Animal data

- No developmental toxicity data
- Mutagenic in *S. typhimurium*, *A. nidulans*, *S. Coelicolor*, Chinese Hamster V79 cells
- No data on carcinogenicity
  - chloroacetaldehyde is considered to be the proximate carcinogenic metabolite of vinyl chloride

Chloroacetaldehyde: Additional data

- No toxicokinetic data with chloroacetaldehyde itself
  - compare metabolic scheme for vinyl chloride
- Mechanism of toxicity
  - only in vitro data without relevance for AEGL-setting
- Highly irritating compound
  - labeled as corrosive in EU

Chloroacetaldehyde: AEGL-setting

Data availability

- No adequate human data
- Animal data indicate that irritation/corrosivity is the major effect of chloroacetaldehyde
  - increasing severity with increasing exposure
  - death due to severe lung damage
  - steep dose-response curve

Chloroacetaldehyde: AEGL-3

TABLE. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat (n=19/20)	10	7 h	0/20	Dow 1952
	25	7 h	19/20	
	50	1 h	0/20	
		2.5 h	20/20	
		4 h	18/20	
	100	0.2 h	0/19	
		2 h	20/20	
	400	0.1 h	1/20	
		0.25 h	20/20	
		0.5 h	19/20	
Rat (n=10)	44	1 h	0/10	TNO 1987
	159		3/10	
	203		4/10	
	243		10/10	
	397		10/10	
	596		10/10	
	2643		10/10	
	203-243	1 h	LC_{50}	

Chloroacetaldehyde: AEGL-3

- *TNO (1987)*
  - point of departure: $BMCL_{05}$ for 1-h exposure to 99 ppm
  - UF=10 (interspecies: 3; intraspecies: 3)
    local effects (direct interaction by parent compound)
    steep concentration-response curve
  - n=1.2 (Dow 1952)

AEGL-3 Values for Chloroacetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
44 ppm (141 mg/m³)	18 ppm (57 mg/m³)	9.9 ppm (32 mg/m³)	3.1 ppm (10 mg/m³)	1.8 ppm (5.6 mg/m³)

Chloroacetaldehyde: AEGL-2

- Rats
  - exposure to chloroacetaldehyde concentrations of 10 to 400 ppm for various durations resulted in labored breathing at higher concentrations (Dow 1952)
  - lung edema in some animals two weeks after a 1-h exposure to 44 ppm (TNO 1987)

Chloroacetaldehyde: AEGL-2

- *TNO (1987)*
  - lung edema in rats two weeks after a 1-h exposure to 44 ppm
  - modifying factor of 2 (LOAEL)
  - UF= 10 (interspecies: 3; intraspecies:3)
  - *n*= 1.2 (from mortality data; similar mode of action)

AEGL-2 Values for Chloroacetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
9.8 ppm (31 mg/m³)	3.9 ppm (13 mg/m³)	2.2 ppm (7.1 mg/m³)	0.69 ppm (2.2 mg/m³)	0.39 ppm (1.5 mg/m³)

Chloroacetaldehyde: AEGL-1

Relevant data regarding AEGL-1 endpoints

- Eye and nasal irritation soon after onset of a single exposure in rats (10 ppm) and guinea pigs (25 ppm)
- Very slight irritation following daily 7-h exposures for 8 days to 5 ppm (no gross pathological effects)
  - UF=10 and n=1.2
  - AEGL-1 values slightly higher than corresponding AEGL-2 values

Chloroacetaldehyde: AEGL-1

- AEGL-1 values considered to be necessary
  - steep concentration-response curve
  - similar mode of action, increasing severity
  - slight irritation expected to precede serious lung effects
  - AEGL-2 values are well-founded
  - AEGL-1 values set at 50% of AEGL-2 values

AEGL-1 Values for Chloroacetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
4.9 ppm (16 mg/m^3)	2.0 ppm (6.3 mg/m^3)	1.1 ppm (3.5 mg/m^3)	0.35 ppm (1.1 mg/m^3)	0.19 ppm (0.62 mg/m^3)

Chloroacetaldehyde: Summary of AEGL-values

Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	4.9 ppm	2.0 ppm	1.1 ppm	0.35 ppm	0.19 ppm
AEGL-2 (Disabling)	9.8 ppm	4.0 ppm	2.2 ppm	0.69 ppm	0.39 ppm
AEGL-3 (Lethal)	44 ppm	18 ppm	9.9 ppm	3.1 ppm	1.8 ppm

ATTACHMENT 15

December 13, 2004

TSD Propionaldehyde

Chemical Manager: M. Payton
Staff Scientist: A. Muller / P.M.J. Bos

Propionaldehyde: Uses

Reactive intermediate in the manufacture of e.g.:

- n-propanol
- propionic acid
- polyethylene additives
- fragrance chemicals
- fungicides

#10

Propionaldehyde: Physical-chemical properties

- Molecular weight: 58.08
- Colorless liquid
- Water solubility: soluble in 5 vol. water
- Boiling point: 49°C
- Odor: suffocating odor
- Flammability: flash point between -18 and -40°C
- LEL: 2.3 - 2.9%

Propionaldehyde: Human data

- No relevant case reports available
- Experiments with volunteers
  - Mild irritation in 12 males exposed to 134 ppm for 30 min

Propionaldehyde: Human data

- No data on reproductive toxicity
- No data on genotoxicity
- No data on carcinogenicity

Propionaldehyde: Animal data

Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	1930 ppm	4 h	No lethality	Eschbach 1981
Rat	8000 ppm	4 h	5/6 deaths	Smyth *et al.* 1951
Rat	25,420 ppm	30 min	LC_{50}	Skog 1950
Rat	Saturated vapor pressure	30 min	4/4 deaths	Gage 1970
Mouse	2868 mg/m^3 (aerosol)	5 h on average	50/50 deaths	Salem and Cullumbine 1960
Rabbit	2868 mg/m^3 (aerosol)	4 h on average	5/5 deaths	Salem and Cullumbine 1960
Guinea pig	2868 mg/m^3 (aerosol)	10 h	3/20 deaths	Salem and Cullumbine 1960

Propionaldehyde: Animal data

Non-lethal toxicity

- Limited acute toxicity data
  - see table
- RD_{50} values
  - rat: 6789 ppm
  - mouse: 2052 ppm
    2078 ppm
    3703 ppm

Propionaldehyde: Animal data

Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	1226 ppm	1 min	No effect on blood pressure	Egle 1972
Rat	4100 ppm	1 min	Increase in blood pressure	Egle 1972
Rat	1930 ppm	4 h	Lachrymation	Eschbach 1981
Mouse	5230 ppm	5 min	Anesthesia	Axelsson *et al.* 1953

Propionaldehyde: Developmental effects

- Rats exposed to 151, 745, 1453 ppm for 6 h/d for 7 d/w (OECD guideline study); Driscoll *et al.* 1993
  - Male and female rats (n=15) exposed starting 2 weeks prior to mating; females exposed up to day 20 of gestation
  - Highest dose males showed systemic effects and local nasal irritation; both types of effects are attributed to repeated exposures
  - No effects on reproductive parameters
  - Reduced pup weight (22%) up to day 4 of lactation at 1500 ppm

Propionaldehyde: Genotoxicity/carcinogenicity

- Genotoxicity
  - Propionaldehyde is genotoxic *in vitro*
  - Results of one *in vivo* study unclear
- Carcinogenicity
  - No data available for propionaldehyde

Propionaldehyde: Kinetic data

- Retention
  - 80% in anesthetized dogs exposed to 164-492 ppm
- Metabolism
  - incorporated into fatty acid metabolism and citric acid cycle
  - conjugation with glutathione

Propionaldehyde versus Acetaldehyde

Comparison of effects of propionaldehyde and acetaldehyde

Effect	Acetaldehyde	Propionaldehyde	Reference
Increase in blood pressure in rat			
5 mg/kg IV (%)	10.7	10.5	Egle *et al.* 1971
10 mg/kg IV (%)	6.7	12.4	
NOEL in ppm for			Egle 1972a
Increased heart rate	5560	4220	
Increased blood pressure	556	1266	
Deposition in dog upper respiratory tract (%)	50-55	59-63	Egle 1972b
Aldehyde dehydrogenase, partially purified from mouse liver cytosol			Petersen *et al.* 1977
Km (uM)	0.59	0.36	
Vmax	4.40	3.30	
RD50 values (ppm)			
B6C3F1 mice	2932	2078	Steinhagen and Barrow 1984
Swiss Webster mice	2845	2052	Steinhagen and Barrow 1984
Swiss Webster mice	4900	2750	Alarie 1981
F-344 rat	2991	6900	Babiuk *et al.* 1985
Mortality	8000 ppm, 8 hour, 0/6 16000 ppm, 8 hour, 0/6	8000 ppm, 4 hour, 5/6	Smyth *et al.* 1951
LC50 in 30 minutes (ppm)	20720	25420	Skog 1950

Propionaldehyde: AEGL-1

Very limited data

- Human data
  - mild irritation in 12 men exposed to 134 ppm for 30 min
- Animal data
  - No relevant data regarding AEGL-1 endpoints

Propionaldehyde: AEGL-1

- *Sim and Pattle (1957)*
  - mild irritation of the mucosal surfaces at 30 min exposure to 134 ppm (n=12)
  - sub AEGL-1 effect
  - UF= 3 (intraspecies factor)
    local effects due to propionaldehyde, therefore, no large differences in kinetics and dynamics expected
  - local irritation: flatlining from 10 min to 8 hours

AEGL-1 Values for Propionaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
45 ppm (108 mg/m³)	45 ppm (108 mg/m³)	45 ppm (108 mg/m³)	45 ppm (108 mg/m³)	45 ppm (108 mg/m³)

Propionaldehyde: AEGL-2

- Rats
  - lachrymation in rats exposed for 4 h to 1930 ppm (starting after 15 min)
  - effects on nasal epithelium upon repeated exposure; considered not relevant for single exposure (highest concentration: 1453 ppm for 6 h/d)
- Mice
  - anesthesia in mice exposed for 5 min to 5230 ppm

Propionaldehyde: AEGL-2

- *Driscoll (1993)*
  - no effects on nasal epithelium in rats after a 6-h single exposure to 1453 ppm
  - UF= 10 (interspecies: 3; intraspecies:3)
    higher factor: values would conflict with human data
    higher factor: values would be inconsistent with acetaldehyde
  - default values of *n*

AEGL-2 Values for Propionaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
330 ppm (800 mg/m³)	330 ppm (800 mg/m³)	260 ppm (630 mg/m³)	170 ppm (410 mg/m³)	110 ppm (270 mg/m³)

Propionaldehyde: Animal data

Summary of Acute Lethal Inhalation Data in Laboratory Animals				
Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	1930 ppm	4 h	No lethality	Eschbach 1981
Rat	8000 ppm	4 h	5/6 deaths	Smyth *et al.* 1951
Rat	25,420 ppm	30 min	LC_{50}	Skog 1950
Rat	Saturated vapor pressure	30 min	4/4 deaths	Gage 1970
Mouse	2868 mg/m³ (aerosol)	5 h on average	50/50 deaths	Salem and Cullumbine 1960
Rabbit	2868 mg/m³ (aerosol)	4 h on average	5/5 deaths	Salem and Cullumbine 1960
Guinea pig	2868 mg/m³ (aerosol)	10 h	3/20 deaths	Salem and Cullumbine 1960

Propionaldehyde: AEGL-3

- Very limited data regarding AEGL-3 endpoints
  - insufficient data for propionaldehyde to derive AEGL-3
  - comparable toxicity profile as with acetaldehyde
    adequate data on AEGL-3 endpoints ($BMDL_{05}$) for acetaldehyde
    AEGL-3 values for acetaldehyde adopted for propionaldehyde

Propionaldehyde: AEGL-3

- *Appelman et al. (1982)*
  - point of departure: $BMDL_{05}$ of 5295 ppm (4-h exposure)
  - UF=10 (interspecies:3; intraspecies: 3)
  - default values for *n* (flatline from 30- to 10-min)

AEGL-3 Values for Propionaldehyde				
10-minute	30-minute	1-hour	4-hour	8-hour
1100 ppm (2700 mg/m³)	1100 ppm (2700 mg/m³)	840 ppm (2000 mg/m³)	530 ppm (1300 mg/m³)	260 ppm (630 mg/m³)

Alternative:
POD: 30-min LC_{50} of 25,420 ppm; MF=3; UF=10; n=1
30-min: 850 ppm; 1-h: 420 ppm; 4-h: 110 ppm; 8-h: 53 ppm

Propionaldehyde: Summary of AEGL-values

Summary of AEGL Values					
	Exposure Duration				
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	45 ppm	45 ppm	45 ppm	45 ppm	45 ppm
AEGL-2 (Disabling)	330 ppm	330 ppm	260 ppm	170 ppm	110 ppm
AEGL-3 (Lethal)	1100 ppm	1100 ppm	840 ppm	530 ppm	260 ppm

Alternative:
POD: 30-min LC_{50} of 25,420 ppm; MF=3; UF=10; n=1
30-min: 850 ppm; 1-h: 420 ppm; 4-h: 110 ppm; 8-h: 53 ppm

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR BIPHENYL

NAC/AEGL-35
December 13-15, 2004
Washington D.C.

ORNL Staff Scientist: Dana F. Glass
Chemical Manager: Richard Thomas
Chemical Reviewers: Susan Ripple and Bob Benson

Biphenyl- Background

- **Currently used as heat-transfer agent and fungistat for citrus**
- **Production greatly decreased due to PCB restrictions**
- **Colorless to pale yellow/white solid at room temperature**
- **Distinct, pleasant odor with low odor threshold**
- **Limited data available on inhalation studies**

Exposure Symptoms

- **Exposures from inhalation or dermal contact**
  - **Eye and throat irritation**
  - **Headaches**
  - **Nausea**

AEGL-1 Values

- AEGL-1 values not recommended
- Lack of data available

AEGL-2 Values

AEGL-2 Values				
10 min	30 min	1 hr	4 hr	8 hr
2.9 ppm	2.9 ppm	2.3 ppm	1.4 ppm	0.73 ppm

- Key Reference:
  - Cannon Laboratories, Inc. 1977
  - National Research Council. 2001

- Endpoint/Concentration/Rationale: Three-fold reduction of AEGL-3 values. Estimated threshold for impaired ability to escape.

AEGL-3 Values

AEGL-3 Values				
10 min	30 min	1 hr	4 hr	8 hr
8.6 ppm	8.6 ppm	6.8 ppm	4.3 ppm	2.2 ppm

- **Key Reference:**
  - **Cannon Laboratories, Inc. 1977**

- **Test Species: 10 male/10 female mice**

- **Exposure: Inhalation: 14, 38 or 43 ppm, 4 hrs**

- **Effect:**
  - **14 ppm: hyperactivity and shallow respiration**
  - **38 and 43 ppm:**
    - **hyperactivity, nasal discharge & rapid respiration. Moderate weight loss (day 1)**
    - **1/10 death- 2 hours at 43 ppm (not compound-related)**
    - **slight lung congestion on gross pathological examination**

- **Endpoint/Concentration/Rationale: 43 ppm- highest concentration used in acute inhalation studies resulting in clinical signs without death**

AEGL-3 Values (cont'd.)

- **Uncertainty Factors/Rationale: 10**

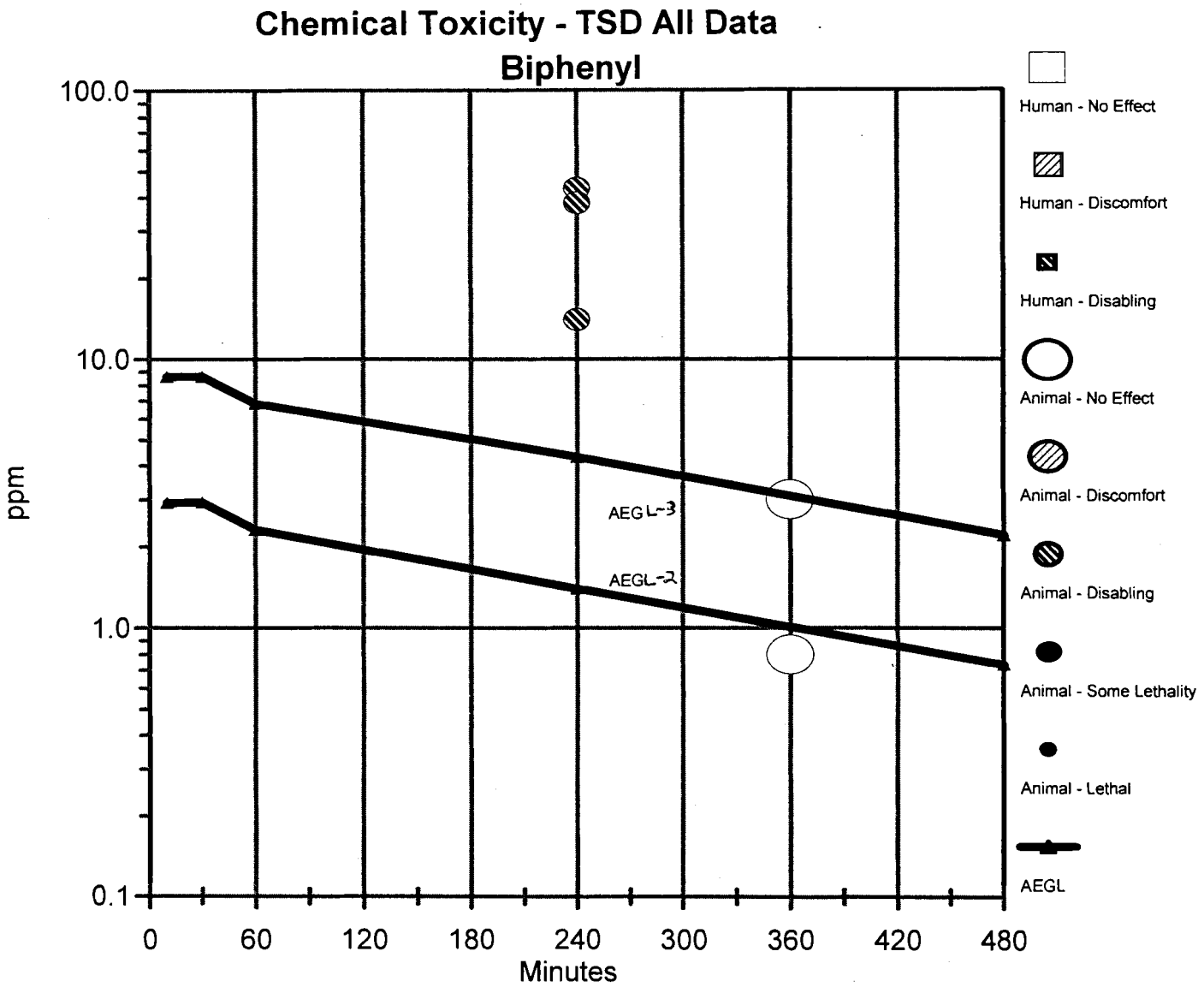
  - Interspecies: 3, clinical signs similar among different species
  - Intraspecies: 3, using intraspecies UF of 10 creates levels unrealistically low compared to occupational levels

- **Time-scaling: Extrapolation to time-points was done**
  - n = 3, for 30 min, 1 hr and 4 hr
  - n = 1, for 8 hr
  - 30-minute AEGL-3 value also adopted as the 10-minute value

Exposure Guidelines
(expressed as ppm)

Extant Standards and Guidelines for Chemical					
Guideline	Exposure Duration				
	10 min	30 min	1 hr	4 hr	8 hr
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.9	2.9	2.3	1.4	0.73
AEGL-3	8.6	8.6	6.8	4.3	2.2
PEL-TWA (OSHA)					0.2
IDLH (NIOSH)		16			
REL-TWA (NIOSH)					0.2 (10 hr)
TLV-TWA (ACGIH)					0.2 (lung)
MAK (Germany)					0.2
MAC (Dutch)					0.2
STV/LLV (Sweden)	0.4 (15 min)				0.2

Time-Scaling



No effect= No effect or mild discomfort
Discomfort= Notable transient discomfort/irritation
Disabling= Irreversible/long lasting effects or impaired ability to escape
Some lethality= Some, but not all, exposed animals died
Lethal= All exposed animals died

ATTACHMENT 17

#12

December 14, 2004

TSD 1,3-Butadiene

Chemical Manager: A. Feldt
Staff Scientist: P.M.J. Bos

Butadiene: Uses

- Production of synthetic rubbers
  - styrene-butadiene rubber; polybutadiene rubber; chloroprene
- Production of plastics
  - acrylonitrile-butadiene-styrene (ABS)

Butadiene: Physical-chemical properties

- Molecular weight: 54.09
- Colorless gas
- Water solubility: 0.735 g/L
- Boiling point: -4.4°C
- Odor: mild aromatic
- Flammability: flashpoint -85°C
- LEL: 2.0%

Butadiene: Human data

- No case reports available
- One relevant study (Carpenter *et al.* 1944)
  - two males were exposed to 2000 (7h), 4000 (6h), or 8000 ppm (8h); one-hour lunch break
  - slight smarting of the eyes; difficulty in focusing at 2000 and 4000 ppm; no effects at 8000 ppm
  - no effects of exposure on performance in tapping test and steadiness test

Butadiene: Human data

Epidemiology

- IARC (1999)
  - limited evidence for the carcinogenicity of 1,3-butadiene in humans
- EC (2002)
  - regarded as carcinogenic to humans (leukemia in SBR workers)
- EPA (2002)
  - cancer risk estimate: 0.08/ppm

Butadiene: Human data

- No relevant data on neurotoxicity or developmental toxicity
- Conflicting or limited evidence for genotoxicity in humans (IARC 1999; WHO 2001; EC 2002)

Butadiene: Animal data

Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rabbit	150,000	25 min	No mortality	Larionov *et al.* (1934)
	250,000	unknown	Mortality	
Guinea pig	50,000	12 h	3/5 deaths	GRPG (1993)
	69,000	2 h	100% survival	
	89,000	10 h	100% mortality	
	200,000	30 min	100% survival	
	200,000	1 h	1/5 deaths	
Rat	50,000	24 h	100% survival	BRPG (1992)
	89,000	6 h	100% survival	
	89,000	10 h	5/7 deaths	
	200,000	30 min	2/5 deaths	
Rat	70,000	4 h	LC_{16}	Shugaev (1969)
	128,000		LC_{50}	
	207,000		LC_{84}	
Rat	2900-4000	15 h	0/2 deaths	Keeling *et al.* (1987)
Mouse	10,000	2 h	100% survival	Bucher *et al.* (1993)
Mouse	91,000	2 h	LC_{16}	Shugaev (1969)
	122,000		LC_{50}	
	169,000		LC_{84}	
Mouse	2000-4000	15 h	lethality	Keeling *et al.* (1987)

Butadiene: Animal data

- No eye effects in rabbits and dogs exposed to 6700 ppm 7.5 h/d for 8 months
- No narcosis in rabbits exposed to 150,000 ppm for 25 min (250,000 ppm was lethal)
- No respiratory stress in pregnant female rats exposed to 7647 ppm (6 h/d)
- Dyspnea during the first 30 min in mice exposed to 4980 ppm (6 h/d for 5 d)

Butadiene: Animal data

- No effects in mice exposed to 10,000 ppm for 2 hours (2-year observation)
- Growth retardation in mice exposed to 1250 (males) or 5000 ppm (females) for 6 h/d, 5 d/w for 2 weeks
- No effects in rats exposed to 8000 ppm (6 h/d; 5 d/w; for 3 months)

Butadiene: Animal data

- Butadiene is genotoxic
- Butadiene is carcinogenic in mice and rats
  - much lower potency in rats than in mice
  - suggested to be a genotoxic carcinogen in mice but carcinogenic via hormonal influences in rats (EC 2002)

Butadiene: Developmental toxicity

- Rats exposed up to 7647 ppm for 6 h/d on day 6-15 (Irish *et al.* 1981)
  - no effects on pregnancy or implantation
  - smaller fetuses with skeletal effects (wavy ribs) due to maternal growth retardation (predominantly at 7647 ppm)
- Rats and mice exposed up to 1000 ppm for 6 h/d on day 6-15 (Hackett *et al.* 1987)
  - rats: maternal growth retardation; no exposure-related fetal effects
  - mice: maternal growth retardation; reduced fetal weight and minor skeletal abnormalities at 200 and 1000 ppm but not at 40 ppm

Butadiene: Developmental toxicity

Conclusions

- Effects are non-specific and occur in the presence of maternal growth retardation
- These effects are unlikely to be due to single exposure (Van Raaij *et al.* 2003)
- Fertility studies with male mice (single exposures) were inconclusive

Butadiene: Additional data

- Mice are much more susceptible than rats
- Large species differences in kinetics between mice and rats
- Higher uptake rate and formation rate of epoxides in mice
- Humans have lower ventilation rate than rats and biotransformation rate is more comparable with rats

Butadiene: AEGL-setting

Data availability

- Acute toxicity of 1,3-butadiene is low, even in mice
- Limited human data available

Butadiene: AEGL-1

Human data:

- One relevant study (Carpenter *et al.* 1944)
  - two males were exposed to 2000 (7h), 4000 (6h), or 8000 ppm (8h)
  - slight smarting of the eyes; difficulty in focusing at 2000 and 4000 ppm; no effects at 8000 ppm
  - no effects of exposure on performance in tapping test and steadiness test
  - *effects on the eyes at 2000 ppm are considered to be sub AEGL-1 effects*

Butadiene: AEGL-1

Animal data

- No eye effects in rabbits and dogs exposed to 6700 ppm 7.5 h/d for 8 months
- No narcosis in rabbits exposed to 150,000 ppm for 25 min
- No respiratory stress in pregnant female rats exposed to 7647 ppm (6 h/d)
- Dyspnea during the first 30 min in mice exposed to 4980 ppm (6 h/d for 5 d)
- No effects in mice exposed to 10,000 ppm for 2 hours (2-year observation)

Butadiene: AEGL-1

Point of departure (Carpenter *et al.* 1944)

- 2000 ppm for 7 hours (very slight effects on the eyes)
- no effects on performance in tapping and steadiness test
- sub AEGL-1 effect (no effects at 8000 ppm)
- UF= 3 (intraspecies factor)
  - local effects due to butadiene, therefore, no large differences in kinetics and dynamics expected
- local irritation: flatlining from 10 min to 8 hours

AEGL-1 Values for Butadiene

10-minute	30-minute	1-hour	4-hour	8-hour
670 ppm (1480 mg/m³)	670 ppm (1480 mg/m³)	670 ppm (1480 mg/m³)	670 ppm (1480 mg/m³)	670 ppm (1480 mg/m³)

Butadiene: AEGL-2

- Human data (Carpenter *et al.* 1944)
  - No effects during 8-h exposure to 8000 ppm
- Animal data
  - No effects in rats exposed to 8000 ppm (6 h/d; 5 d/w; for 3 months)
  - No effects in mice exposed to 10,000 ppm for 2 hours (2-year observation)
  - Growth retardation in mice exposed to 1250 (males) or 5000 ppm (females) for 6 h/d, 5 d/w for 2 weeks
  - No narcosis in rabbits exposed to 150,000 ppm for 25 min (250,000 ppm was lethal)
  - ~~No developmental effects due to single exposure~~

Butadiene: AEGL-2

Point of departure (Crouch *et al.* 1979)

- *No effects in rats exposed to 8000 ppm* (6 h/d; 5 d/w; for 3 months)
- UF=3
  - highest concentration tested
  - repeated exposure
  - higher factor: values would conflict with human data
- default values of n: 10-min value equal to 30-min value

AEGL-2 Values for Butadiene

10-minute	30-minute	1-hour	4-hour	8-hour
6100 ppm[¶] (13,500 mg/m³)	6100 ppm[¶] (13,500 mg/m³)	4800 ppm[¶] (10,600 mg/m³)	3100 ppm[¶] (6850 mg/m³)	2000 ppm[¶] (4420 mg/m³)

¶ All proposed values are higher than or equal to 10% of the lower explosive limit of butadiene in air (LEL = 2% (20,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

Butadiene: AEGL-3

- No adequate human data
- Animal data: Shugaev (1969)
  - mice: 2-h LC_{50} of 122,000 ppm
  - rats: 4-h LC_{50} of 128,000 ppm (LC_{01}: 41,000 ppm)

Butadiene: AEGL-3

Point of departure (Shugaev 1969)

- LC_{01} of 41,000 ppm in rats
- UF=3
  - higher factor: values would conflict with human data
  - higher factor: values would be very close to AEGL-2 values
- default values of n; 10-min value equal to 30-min value

Butadiene: AEGL-3

AEGL-3 Values for Butadiene				
10-minute	30-minute	1-hour	4-hour	8-hour
See below*	See below*	See below*	See below*	6800 ppm¶ (15,000 mg/m³)

* The calculated AEGL-3 values for 10-min, 30-min, and 1-h are higher than the lower explosive limit of butadiene in air (LEL = 2% (20,000 ppm)). The calculated AEGL-3 values for 4 –h is higher than 50% of the lower explosive limit of butadiene in air. Therefore, extreme safety considerations against hazard of explosion must be taken into account.

The respective calculated AEGL-3 values for 10-min, 30-min, 1-h, and 4-h are: 27,000 ppm (59,700 mg/m³), 27,000 ppm (59,700 mg/m³), 22,000 ppm (48,620 mg/m³), and 14,000 ppm (30,900 mg/m³).

¶ The proposed value for the 8-hour exposure period is higher than 10% of the lower explosive limit of butadiene in air. Therefore, safety considerations against hazard of explosion must be taken into account.

#12

Butadiene: Summary of AEGL-values

Summary of AEGL Values					
	Exposure Duration				
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	670 ppm	670 ppm	670 ppm	670 ppm	670 ppm
AEGL-2 (Disabling)	6100 ppm¶	6100 ppm¶	4800 ppm¶	3100 ppm¶	2000 ppm¶
AEGL-3 (Lethal)	See below*	See below*	See below*	See below*	6800 ppm¶

* The calculated AEGL-3 values for 10-min, 30-min, and 1-h are higher than the lower explosive limit of butadiene in air (LEL = 2% (20,000 ppm)). The calculated AEGL-3 values for 4 –h is higher than 50% of the lower explosive limit of butadiene in air. Therefore, extreme safety considerations against hazard of explosion must be taken into account.

The respective calculated AEGL-3 values for 10-min, 30-min, 1-h, and 4-h are: 27,000 ppm (59,700 mg/m³), 27,000 ppm (59,700 mg/m³), 22,000 ppm (48,620 mg/m³), and 14,000 ppm (30,900 mg/m³).

¶ The proposed value is higher than 10% of the lower explosive limit of butadiene in air. Therefore, safety considerations against hazard of explosion must be taken into account.

Table 1 - Chemical and Physical Properties #11

Parameter	Value	Reference
Synonyms	DMA; *N*-methylmethanamine; methanamine N-methyl	Bingham et al., 2001
Chemical formula	C_2H_7N	Bingham et al., 2001
Molecular weight	45.08	Bingham et al., 2001
CAS Reg. No.	124-40-3	Bingham et al., 2001
Physical state	Colorless gas	Steinhagen et al., 1982
Solubility in water	Very soluble	Bingham et al., 2001
Vapor pressure	2 atm	Bingham et al.,2001
Vapor density (air =1)	1.55	Bingham et al.,2001
Liquid density (water =1)	0.6804 g/mL	Bingham et al.,2001
Melting point	-93 °C	Bingham et al., 2001
Boiling point	7.4 °C	Bingham et al., 2001
Odor threshold	1.6 ppm; smell of rotting fish	Bingham et al., 2001
Flammability limits	2.8 through 14.4%	www.east-westglobal.com
Conversion factors	1 ppm = 1.84 mg/m^3	Bingham et al., 2001

Table 2 - Main Parameters of Acute Inhalation Toxicity of Dimethylamine

Species	Concentration (ppm)	Exposure Time (hours)	Effect	References
Rats	4,700	4	LC_{50}	Koch et al., 1980
Rats	4,540	6	LC_{50}	Steinhagen et al., 1982
Mice	4,725	2	LC_{50}	Mezentseva, 1956

Table 3 - Summery of Nonlethal Inhalation Data on Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	References
Rats	573	10- min	RD_{50}	Steinhagen et al., 1982
Mice	511	10-min	RD_{50}	Steinhagen et al., 1982
Rats	175	6-hour	Discharge of modified mucus	Gross et al., 1987
Rats / Mice	100	10-min	Mild levels of discomfort	Steinhagen et al., 1982

Table 4 - AEGL-1 Values for Dimethylamine

10-minute	30-minute	1-hour	4-hour	8-hour
3.3 ppm 6.1 (mg/m^3)	3.3 ppm 6.1 (mg/m^3)	3.3 ppm 6.1 (mg/m^3)	3.3 ppm 6.1 (mg/m^3)	3.3 ppm 6.1 (mg/m^3)

Derivation of AEGL-1

Key Study:	Steinhagen et al. (1982). Single Intake of DMA in at Concentrations of 100 ppm and Higher for 10 minutes in Rats and Mice caused minimal reversible changes determined as "MILD" LEVELS OF DISCOMFORT (hyperemia in the mucous and discharge from nasal routs) in the absence of any pathomorphological modifications.
Toxicity Endpoint:	Increase in level of single exposure to the substance at concentrations of 175 – 200 ppm caused a wide spectrum fo disorders from epithelial vacuolization to reversible ulceration or chronic inflammation. Secretion of modified mucus was observed (Gross et al., 1987; Steinhagen et al., 1982). Lowering the levels of chronic DMA inhalation exposure of rats to (10 and 30 ppm) did not lead to any histopathological changes (CIIT, 1982).
Uncertainty Factors:	In order to account for interspecies variability of DMA induced rhinitis an uncertainty factor of 10 was used. UF 3 was used to account for intraspecies variability. Based on the fact that in deriving AEGL-1 the starting point was reversible rhinitis in rats in rats exposed to DMA at 100 ppm concentration for 10 minutes, further lowering the values seems to be unjustified.
Scaling Process:	was not done
Time Scaling:	was not done
Calculations:	
10-min AEGL-1	100 ppm/30 = 3.3 ppm
30-min AEGL-1	100 ppm/30 = 3.3 ppm
1-hour AEGL-1	100 ppm/30 = 3.3 ppm
4-hour AEGL-1	100 ppm/30 = 3.3 ppm
8-hour AEGL-1	100 ppm/30 = 3.3 ppm

Table 5 - AEGL-2 Values for Dimethylamine

10-minute	30-minute	1-hour	4-hour	8-hour
19.3 ppm 35.6(mg/m^3)	13.4 ppm 24.7mg/m^3)	10.6 ppm 19.5(mg/m^3)	6.7 ppm 12.4(mg/m^3)	4.4 ppm 8.1(mg/m^3)

Derivation of AEGL-2

Key Study: Gross et al. (1987). Single 6-hour exposure of male rats to dimethylamine at the concentration of 175 ppm caused a wide spectrum of disorders from epithelial vacuolization to ulceration and acute or chronic inflammation. No irreversible histological disorders were observed.

Toxicity Endpoint: Increase of DMA chronic inhalation exposure level up to 185 ppm concentration caused clinical signs in the form of central lobular degeneration (Hollingsworth, R. L. and Rowe, V. K., 1964).
Lowering the levels of chronic DMA inhalation exposure of rats to (10, 30, and 100 ppm) did not lead to any histopathological changes (CIIT, 1982).

Uncertainty Factors: In order to account for interspecies variability of DMA induced rhinitis, erosion of anterior edges, and fenestration of limiting layer an uncertainty factor of 10 was used. UF 3 was used to account for intraspecies variability.

Scaling process: $C^1 \times t = k$ (ten Berge et al., 1986); 175 ppm/30 = 5,833 ppm
$C^3 * t = k$; $(5{,}833\ ppm)^3 * 360\ min = 71{,}458.333\ ppm^3 * min$
$C^1 * t = k$; 5,833 ppm * 360 min = 2,099.88 ppm * min

Time scaling: The relation of exposure concentration and exposure time for most irritants and for vapors and gases of systemic action can be described as follows: $C^n * t = k$, where the exponent n varies from 0.8 to 3.5 (ten Berge et al, 1986). Using n=3 for cases of extrapolation on a shorter exposure time and n=1 is used for extrapolation on a longer exposure.

Calculations:

10-min AEGL-1 $C^3 * 10\ min = 71458.333\ ppm^3 * min$; C = 19.3 ppm

30-min AEGL-1 $C^3 * 30\ min = 71458.333\ ppm^3 * min$; C = 13.4 ppm

1-hour AEGL-1 $C^3 * 60\ min = 71458.333\ ppm^3 * min$; C = 10.6 ppm

4-hour AEGL-1 $C^3 * 240\ min = 71458.333\ ppm^3 * min$; C = 6.7 ppm

8-hour AEGL-1 $C^1 * 480\ min = 2099.88\ ppm * min$; C = 4.4 ppm

Table 6 - AEGL-3 Values for Dimethylamine

10-minute	30-minute	1-hour	4-hour	8-hour
275.2 ppm 507.4(mg/m^3)	190.8 ppm 351.8(mg/m^3)	151.4 ppm 279.1(mg/m^3)	95.4 ppm 175.9(mg/m^3)	62.5 ppm 115.2(mg/m^3)

Derivation of AEGL-3

Key Study: Steinhagen et al., 1982 was based on determining the threshold by the lethal effect of 2,500 ppm followed by severe injuries in respiratory tract and a number of other internal organs.

Toxicity Endpoint: Increase of exposure level to the substance up to 2,800 ppm causes minimal lethality effect; while DMA exposure at 4,540 ppm concentration is the mean lethal level (Steinhagen et al., 1982).

Uncertainty Factors: Based on LC_{50} values an uncertainty factor of 10 was used to account for interspecies variability of DMA induced toxicity. Intraspecies variability was limited by a factor of 3 since in majority of individuals exposure of respiratory tract and a number of internal organs is manifested in similar boundaries and with similar sensitivity. Based on the fact that in deriving AEGL values non-lethal toxic effect followed by severe injuries in respiratory tract and number of internal organs was the starting point further decrease of the values was not justified.

Scaling process: C^1 x t = k (ten Berge et al., 1986); 2,500 ppm/30 = 83.33 ppm
C^3 * t = k; (83.33 ppm)^3 * 360 min = 208308334.3 ppm^3 min
C^1 * t = k; 83.33 ppm * 360 min = 29998.8 ppm * min

Time scaling: Relation of concentration and exposure time for most irritants and for vapors and gases with systemic action can be described as follows: C^n * t = k, where the exponent n varies from 0.8 to 3.5 (ten Berge et al., 1986). Due to absence of specific data intermediary scaling was done by formula C^n * t = k with use of n=3 for extrapolation cases on shorter exposures; and n=1 was used for extrapolation on shorter exposure.

<u>Calculations:</u>

<u>10-min AEGL-1</u>	C^3 * 10 min = 208308334.3 ppm^3 * min;	C = 275.2 ppm
<u>30-min AEGL-1</u>	C^3 * 30 min = 208308334.3 ppm^3 * min;	C = 190.8 ppm
<u>1-hour AEGL-1</u>	C^3 * 60 min = 208308334.3 ppm^3 * min;	C = 151.4 ppm
<u>4-hour AEGL-1</u>	C^3 * 240 min = 208308334.3 ppm^3 * min;	C = 95.4 ppm
<u>8-hour AEGL-1</u>	C^1 * 480 min = 29998.8 ppm * min;	C = 62.5 ppm

Table 7 - Extant Standards and Guidelines for Dimethylamine

Exposure Duration	Exposure Duration				
	10-minute	**10-minute**	**10-minute**	**10-minute**	**10-minute**
AEGL-1	3.3 ppm 6.1 (mg/m^3)	3.3 ppm 6.1 (mg/m^3)	3.3 ppm 6.1 (mg/m^3)	3.3 ppm 6.1 (mg/m^3)	3.3 ppm 6.1 (mg/m^3)
AEGL-2	19.3 ppm 35.6(mg/m^3)	13.4 ppm 24.7(mg/m^3)	10.6 ppm 19.5(mg/m^3)	6.7 ppm 12.4(mg/m^3)	4.4 ppm 8.1 (mg/m^3)
AEGL-3	275.2 ppm 507.4(mg/m^3)	190.8 ppm 351.8(mg/m^3)	151.4 ppm 279.1(mg/m^3)	95.4 ppm 175.9(mg/m^3)	62.5 ppm 115.2(mg/m^3)
ERPG-1 (AIHA)			0.6 ppm		
ERPG-2 (AIHA)			100 ppm		
ERPG-3 (AIHA)			350 ppm		
EEGL (NRC)					
PEL-TWA (OSHA)					10 ppm (18 mg/m^3)
PEL-STEL (OSHA)					10 ppm
IDLH (NIOSH)		2,000 ppm			
REL-TWA (NIOSH)					10ppm (18 mg/m^3)
REL-STEL (NIOSH)					
TLV-TWA (ACGIH)					5 ppm (9.2 mg/m^3)
TLV-STEL (ACGIH)	15 ppm (27.6mg/m^3)				
MAK Peak Limit (Germany)	2 ppm (3.7) mg/m^3				
MAC (Nederland's)					1 ppm (1.8) mg/m^3.

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR ETHYL MERCAPTAN

NAC/AEGL-35
December 13-15, 2004
Washington, D. C.

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Iris Camacho

Chemical Reviewers: Steve Barbee and George Rusch

Mechanism of Toxicity

Acts similarly to hydrogen sulfide, methyl mercaptan and cyanide

Interrupts electron transport through inhibition of cytochrome oxidase

Relative Toxicity (Rat Lethality Data)

Acute toxicity of ethyl mercaptan is much less than that of

Methyl mercaptan

Hydrogen sulfide

Acute toxicity of methyl mercaptan is similar to or slightly less than that of hydrogen sulfide

4-Hour Rat LC_{50} Values (Tansy et al., 1981)	
Ethyl Mercaptan	4740 ppm
Methyl Mercaptan	675 ppm
Hydrogen Sulfide	444 ppm

AEGL-1 VALUES: ETHYL MERCAPTAN				
10 minute	30 minute	1 hour	4 hour	8 hour
1 ppm	1 ppm	1 ppm	1 ppm	1 ppm

Species: Rabbit
Concentration: 10 ppm
Time: 20 minutes
Endpoint: NOEL for Irritation
Reference: Shibata, 1966b

Time Scaling: Values held constant across time because minor irritation does not vary greatly over time.

Uncertainty Factors:

Interspecies = 3

Intraspecies = 3

Use of the full factor of 10 for either interspecies or intraspecies variability would yield AEGL-1 values ≤0.3 ppm which is inconsistent with the available human data. No mucosal irritation was noted in humans exposed to 0.4 ppm ethyl mercaptan 3 hours/day for 5 or 10 days (Blinova,1965).

AEGL-2 VALUES: ETHYL MERCAPTAN				
10 minute	30 minute	1 hour	4 hour	8 hour
150 ppm	150 ppm	120 ppm	77 ppm	37 ppm

Endpoint:

Three-fold reduction of AEGL-3 values. Estimated threshold for the inability to escape.

Reference:

Time Scaling: See AEGL-3 derivation.

Uncertainty Factors:

Interspecies = 3 See AEGL-3 justification.

Intraspecies = 3 See AEGL-3 justification.

AEGL-3 VALUES: ETHYL MERCAPTAN				
10 minute	30 minute	1 hour	4 hour	8 hour
450 ppm	450 ppm	360 ppm	230 ppm	110 ppm

Species: Mouse
Concentration: 2250 ppm
Time: 4 hours
Endpoint: LC_{01} (Estimated threshold for death. Used instead of $BMCL_{05}$ for consistency with methyl mercaptan)
Reference: Fairchild and Stokinger, 1958

Time Scaling: $c^n \times t = k$, where the exponent, n, is the conservative default of 1 (8-hr) or 3 (30-min, 1-hr, 4-hr). The 30-min value is adopted as the 10-min AEGL-3 value.

Uncertainty Factors:
Interspecies = 3 The mouse is the most sensitive species.

Intraspecies = 3 Considered sufficient due to the steepness of the lethal response curve which implies limited individual variability.

<u>Mouse (4-hr):</u>
2600 ppm: 40% lethality
2770 ppm: LC_{50}
3573 ppm: 100% lethality

<u>Rat (4-hr):</u>
3808 ppm: LC_{01}
4740 ppm: LC_{50}

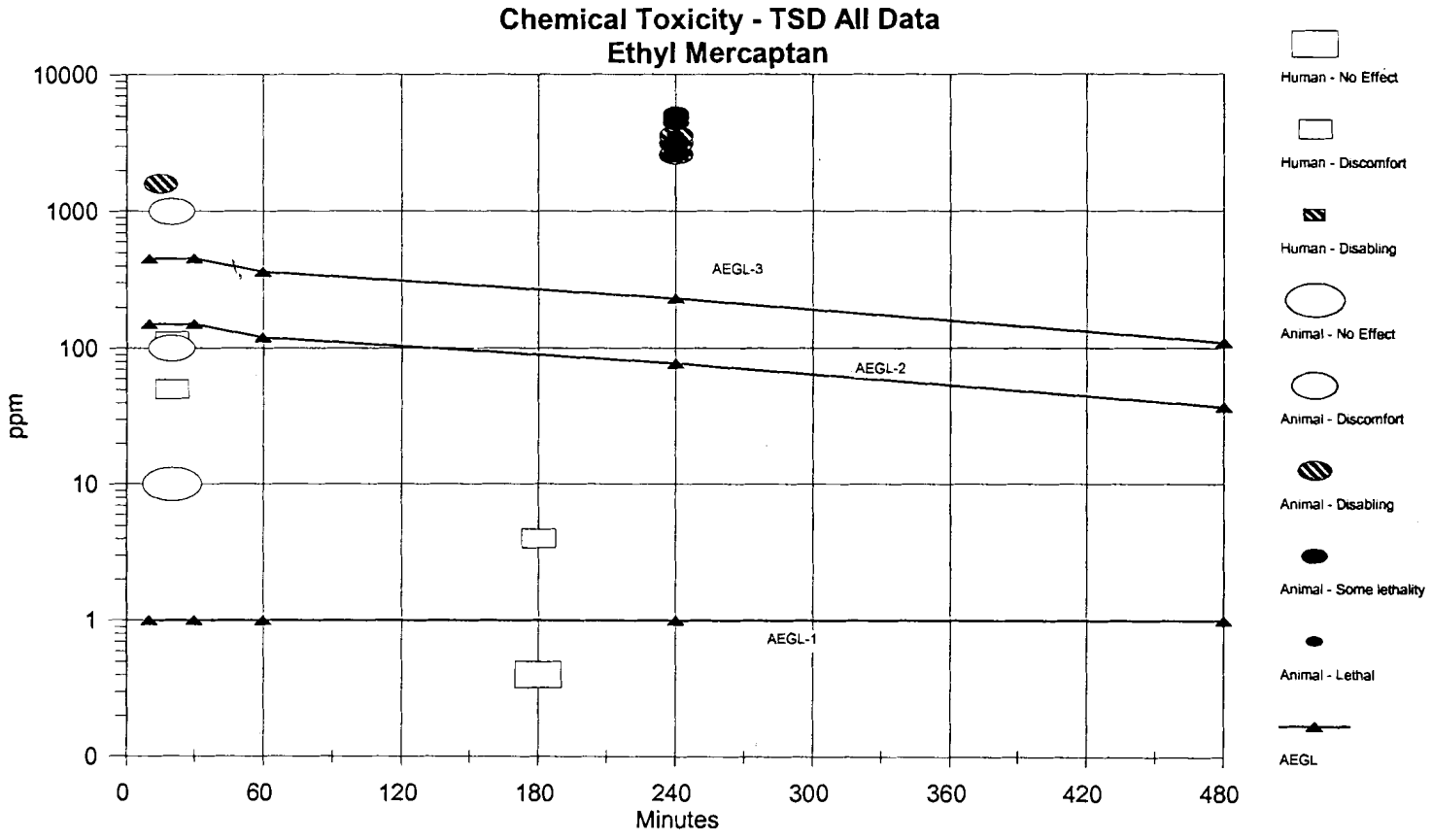
<u>Support for Total UF of 10:</u>
A total UF of 30 would yield AEGL-3 values inconsistent with the total data set.

Values would approach AEGL-3 values derived for hydrogen sulfide
8-hr H_2S AEGL-3 = 31 ppm
8-hr ethyl mercaptan AEGL-3 would be 37 ppm

Ethyl mercaptan is less toxic than hydrogen sulfide, [the 4-hour rat LC_{50} value for ethyl mercaptan was 4740 ppm. The 4-hour LC_{50} value for hydrogen sulfide was 444 ppm]

A 30-minute AEGL-3 of 150 ppm would be derived. Humans exposed to 112 ppm ethyl mercaptan for 20 minutes exhibited only a slightly irregular, and decreased breathing rate.

Extant Standards and Guidelines for Ethyl Mercaptan					
Guideline	**Exposure Duration**				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
AEGL-2	150 ppm	150 ppm	120 ppm	77 ppm	37 ppm
AEGL-3	450 ppm	450 ppm	360 ppm	230 ppm	110 ppm
NIOSH IDLH		500 ppm			
NIOSH REL	0.5 ppm				
OSHA PEL					10 ppm (ceiling)
ACGIH-TLV TWA					0.5 ppm
MAK (German)					0.5 ppm
MAC (Dutch)					0.5 ppm


Chemical Toxicity - TSD All Data
Ethyl Mercaptan
10000
1000
100
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some lethality
Animal - Lethal
AEGL

Derivation of the Level of Distinct Odor Awareness (LOA)

The odor detection threshold (OT_{50}): 0.00076 ppm (Amoore and Hautala (1983).

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$I = k_w \times \log (C / OT_{50}) + 0.5$

For the Fechner coefficient, the default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$3 = 2.33 \times \log (C / 0.00076) + 0.5$ which can be rearranged to
$\log (C / 0.00076) = (3 - 0.5) / 2.33 = 1.07$ and results in
$C = (10^{1.07}) \times 0.00076 = 0.0089$ ppm

$LOA = C \times 1.33 = 0.0089 \text{ ppm} \times 1.33 = 0.011837$ ppm

The LOA for ethyl mercaptan is 0.012 ppm.

ATTACHMENT 20

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

NITROGEN MUSTARDS
(HN1 CAS Reg. No. 538-07-8)
(HN2 CAS Reg. No. 51-75-2)
(HN3 CAS Reg. No. 555-77-1)

December 13-16, 2004

Nitrogen Mustards - Nonlethal Toxicity in Humans

- eyes are sensitive target [similar to agent HD (sulfur mustard)]

- respiratory tract effects possible but not reported at exposures inducing ocular effects

Estimated effect thresholds in humans exposed to nitrogen mustard vapors.			
HN1	HN2	HN3	Effect
-	0.012 mg-min/m^3	-	No observable effect level during therapeutic use of HN2 (Van Vloten et al., 1993)
90 mg-min/m^3	70 mg-min/m^3	42 mg-min/m^3	Moderate but reversible ocular effects (Porton report, 1942a, 1943d; U.S. Army Med. Div., 1945c,d; NDRC, 1946)
>21,170 mg-min/m^3	5800 mg-min/m^3	1800 mg-min/m^3 1300 mg-min/m^3	Median blistering Ct (10-min or 20-min exposure) for normal skin Median blistering Ct (20-min exposure) for sweating skin (NDRC, 1944)

Nitrogen Mustards - Lethal Toxicity in Humans

- **No quantitative data regarding lethal toxicity of HN**

Nitrogen Mustards - Nonlethal Toxicity in Animals

- **Studies in animals focused on lethality; no information available regarding nonlethal effects**

Nitrogen Mustards - Lethal Toxicity in Animals

- **LCt_{50} values for multiple species; various concentrations and durations**

  - **HN1**

Monkey:	**1500 mg-min/m^3**
Dog:	**800 mg-min/m^3**
Rat:	**750-1200 mg-min/m^3**
Mouse:	**900-1300 mg-min/m^3**
Rabbit:	**900->4000 mg-min/m^3**
Cat:	**400 mg-min/m^3**
Guinea pig:	**1500-3000 mg-min/m^3**

  - **HN2**

Dog:	**2000 mg-min/m^3**
Rat:	**600-4000 mg-min/m^3**
Mouse:	**1500-7000 mg-min/m^3**
Rabbit:	**1000-8000 mg-min/m^3**
Guinea pig:	**>1200-8000 mg-min/m^3**

Nitrogen Mustards - Lethal Toxicity in Animals

- **HN3**

Dog:	**400-1500 mg-min/m^3**
Rat:	**670-1700 mg-min/m^3**
Mouse:	**165-600 mg-min/m^3**
Rabbit:	**500-3000 mg-min/m^3**
Cat:	**400 mg-min/m^3**
Guinea pig:	**>1000->23000 mg-min/m^3**

Nitrogen Mustards - Data Evaluation/Study Selection Criteria

- analytical vs nominal exposure concentrations
- exposure duration data
- number of animals
- post-exposure observation period
- environmental conditions (temp., humidity)
- species sensitivity

Nitrogen Mustards - Special Considerations

- **Metabolism/Disposition**
  - **dermal penetration of HN vapor**
    - **linear with time**
    - **enhanced with increasing temperature & humidity**

- **Mechanism of action**
  - **formation of immonium ion which is reactive with nucelophiles**
  - **all HN alkylators**
  - **precise mechanism unclear**

Summary of AEGL Values for Nitrogen Mustards (mg/m^3)					
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)					
HN1	**NR[a]**	**NR[a]**	**NR[a]**	**NR[a]**	**NR[a]**
HN2	**NR[a]**	**NR[a]**	**NR[a]**	**NR[a]**	**NR[a]**
HN3	**NR[a]**	**NR[a]**	**NR[a]**	**NR[a]**	**NR[a]**
AEGL-2 (Disabling)					
HN1	**0.90**	**0.30**	**0.15**	**0.038**	**0.019**
HN2	**0.55**	**0.18**	**0.092**	**0.023**	**0.011**
HN3	**0.42**	**0.14**	**0.070**	**0.018**	**0.0088**
AEGL-3 (Lethality)					
HN1	**1.8**	**0.96**	**0.48**	**0.12**	**0.060**
HN2	**1.3**	**0.88**	**0.70**	**0.28**	**0.14**
HN3	**2.2**	**0.74**	**0.37**	**0.093**	**0.047**

AEGL-2 VALUES FOR HN1				
10 minutes	30 minutes	1 hour	4 hours	8 hours
0.90 mg/m^3	0.30 mg/m^3	0.15 mg/m^3	0.038 mg/m^3	0.019 mg/m^3

Reference: Porton Report. 1943d. The effects of HN1 vapour on human and rabbit eyes. No. 2563. November 18, 1943. Cited in NDRC, 1946.

Test Species/Strain/Sex/Number: Human volunteers/males/21

Exposure Route/Concentrations/Durations: ocular exposure to vapors; CT determined based upon exposure durations of 5 to 67 minutes.

Effects: Ocular irritation in human volunteer subjects; lacrimation, feeling of grittiness in eyes, belpharospasm, photophobia, conjunctival injection.

Endpoint/Concentration/Rationale: 90 mg-min/m^3 based upon exposure durations of 5-67 minutes.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: none; human subjects
Intraspecies: 3; intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.

Modifying Factor: 3; some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. Therefore, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: For the 10-min., 30-min, and 1-hr AEGL-2, concentrations determined directly from cumulative exposure threshold value of 90 mg-min/m^3. The exposure concentration-time relationship for longer durations (e.g., the 4-hr and 8-hr AEGL time points) is uncertain and an empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating from the 60-minute experimental exposure of 1.5 mg/m^3 period to the 4-hour and 8-hour AEGL-2 time periods resulting in exposures of 0.38 mg/m^3 and 1.88 mg/m^3.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. The data are considered appropriate for setting AEGL-2 values for HN1.

AEGL-3 VALUES FOR HN1				
10 minutes	30 minutes	1 hour	4 hours	8 hours
1.8 mg/m^3	0.96 mg/m^3	0.48 mg/m^3	0.12 mg/m^3	0.060 mg/m^3

Reference: U.S. Army Medical Division. 1945a. Medical Division monthly progress report. September, 1945. Cited in NRDC, 1946.

Test Species/Strain/Sex/Number: 84 male rats

Exposure Route/Concentrations/Durations: inhalation/experimental exposure durations of 20-100 minutes/ analytically determined concentrations.; 90°F chamber temp., 10-15 day observation period

Effects: Lethality response data only

Endpoint/Concentration/Rationale: Lethality threshold of 287 mg-min/m^3 in rats estimated by 3-fold reduction of inhalation LCt_{50} of 860 mg-min/m^3

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

- Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.
- Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

AEGL-2 VALUES FOR HN2				
10 minutes	30 minutes	1 hour	4 hours	8 hours
0.55 mg/m^3	0.18 mg/m^3	0.092 mg/m^3	0.023 mg/m^3	0.011 mg/m^3

Reference: Porton Report. 1942a. On the action of S on the eye; its comparison with allied compounds and with H. No. 2402. August 7, 1942. Cited in NDRC, 1946

Test Species/Strain/Sex/Number: Human male volunteers/number not specified

Exposure Route/Concentrations/Durations: 10-55 mg/m^3; exposure durations of 0.5 min to 10 min.; Ct values of 40-55 mgpmin/m^3; subjects wore oronasal masks

Effects: ocular irritation following exposure (grittiness in eyes; photophobia, belpharospasm; ocular pain).

Endpoint/Concentration/Rationale: 55 mg-min/m^3 considered threshold for inducing military fine-skill operational ineffectiveness

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: none; human subjects
Intraspecies: 3; intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.

Modifying Factor: 3. Some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. Therefore, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: For the 10-min. AEGL-2, concentrations were determined directly from cumulative exposure threshold value of 55 mg-min/m^3. The exposure concentration-time relationship for remaining AEGL-specific time points durations is uncertain and an empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating to these time points.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. The data are considered appropriate for setting AEGL-2 values for HN2.

Time Scaling:	$C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The exposure concentration-time relationship for many irritant and systemically acting vapors and gases may described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). For 10-min. AEGL-3: point-of-departure based upon estimated lethality threshold of 287 mg-min/m^3 resulting from 20-minute exposure (14.4 mg/m^3) (14.4 mg/m^3)^3 x 20 min. = 59,719 mg-min/m^3
Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species exposed to high temperature conditions optimal for enhancing HN1 activity (i.e., worst-case scenario). A 10 to15-day post exposure observation period accounted for kown latency in toxic responses to HN1	

AEGL-3 VALUES FOR HN2				
10 minutes	30 minutes	1 hour	4 hours	8 hours
1.3 mg/m^3	0.88 mg/m^3	0.70 mg/m^3	0.28 mg/m^3	0.14 mg/m^3

Reference: Porton Report. 1943b. Toxicity of S vapour. Further experiments on the exposure of animals to S vapour. No. 2464. February 9, 1943. Cited in NDRC, 1946.

Test Species/Strain/Sex/Number: rat/gender not specified/56

Exposure Route/Concentrations/Durations: inhalation/experimental exposure durations of 120-360 minutes resulting in cumulative exposures of 2000 mg-min/m^3

Effects: Lethality only

Endpoint/Concentration/Rationale: Lethality threshold of 667 mg-min/m^3 in rats estimated by 3-fold reduction of LCt_{50} of 2000 mg-min/m^3.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.

Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling:	**$C^n x\ t = k$; data were unavailable for empirical derivation of a scaling factor. The concentration-time relationship for many irritant and systemically acting vapors and gases may described by $C^n x\ t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $Cn\ x\ t = k$ equation (NRC, 2001).** **For 10-min., 30-min, and 1-hr AEGL-3: point-of-departure based upon estimated lethality threshold of 667 mg-min/m^3 resulting from 120-minute exposure (5.56 mg/m^3)** **(5.56 mg/m^3)^3 x 120 min. = 20,625.6 mg-min/m^3**
Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species. A 14-day post exposure observation period accounted for known latency in toxic responses to HN2.	

AEGL-2 VALUES FOR HN3				
10 minutes	30 minutes	1 hour	4 hours	8 hours
0.42 mg/m^3	0.14 mg/m^3	0.070 mg/m^3	0.018 mg/m^3	0.0088 mg/m^3

Reference: U.S. Army Medical Division. 1945c. Medical Division monthly progress report. March, 1945. Cited in NRDC, 1946.
U.S. Army Medical Division. 1945d. Medical Division monthly progress report. February, 1945. Cited in NRDC, 1946.

Test Species/Strain/Sex/Number: Human volunteer subjects/male/7

Exposure Route/Concentrations/Durations: inhalation/20-40 mg-min/m^3; 7 min.

Effects: exposure to 20 mg-min/m^3 (duration not specified) resulted in conjunctival injection and corneal edema with no symptoms being reported by subjects
exposure to 40-mg-min/m^3 produced lacrimation, feeling of grittiness, photophobia, marked conjunctival injection

Endpoint/Concentration/Rationale:40-mg-min/m^3 considered threshold for compromised task efficiency.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: human subjects, none applied
Intraspecies: adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.
Intraspecies:

Modifying Factor: 3; some of the tests may have been performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. Therefore, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: The exposure-time response relationship for AEGL-specific time points durations is uncertain and an empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating from the 7-minute experimental period to the AEGL-specific time points.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. Although the short exposure duration results in extensive extrapolation, an *n* of 1 was applied to provide more conservative exposure concentration estimates. Furthermore, the critical effect is a conservative point-of-departure for AEGL-2 severity effects. The data are considered appropriate for setting AEGL-2 values for HN3.

AEGL-3 VALUES FOR HN3				
10 minutes	30 minutes	1 hour	4 hours	8 hours
2.2 mg/m^3	0.74 mg/m^3	0.37 mg/m^3	0.093 mg/m^3	0.047 mg/m^3

Reference: Porton Report, 1943c. Toxicity and pathology of HN3. No. 2548. November 18, 1944. Cited in NDRC, 1946

Test Species/Strain/Sex/Number: 69 rats/gender not specified/exposure group

Exposure Route/Concentrations/Durations: inhalation LCt_{50} of 670 mg-min/m^3; exposure durations of 10-100 min.

Effects: Lethality response data only

Endpoint/Concentration/Rationale: Lethality threshold of 223.3 mg-min/m3 in rats estimated by 3-fold reduction of LCt_{50} of 670 mg-min/m3; experimental exposure durations of 10-100 minutes.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.

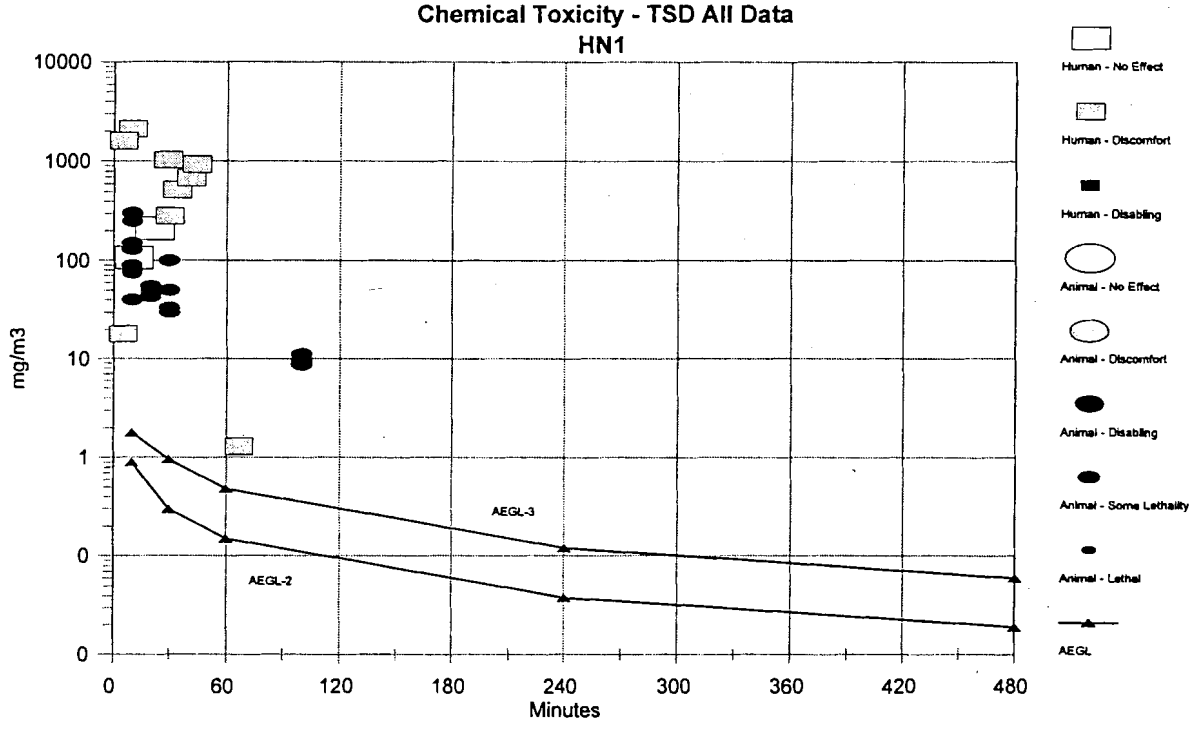
Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Point-of-departure concentrations for each AEGL time point were determined directly from cumulative exposure threshold value of 223.3 mg-min/m^3. This is effectively the use of $n = 1$ for $C^n x\, t = k$.

Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species and a chamber temperature (85°F) which would represent a worst-case scenario. A 15-day post exposure observation period accounted for kown latency in toxic responses to HN3.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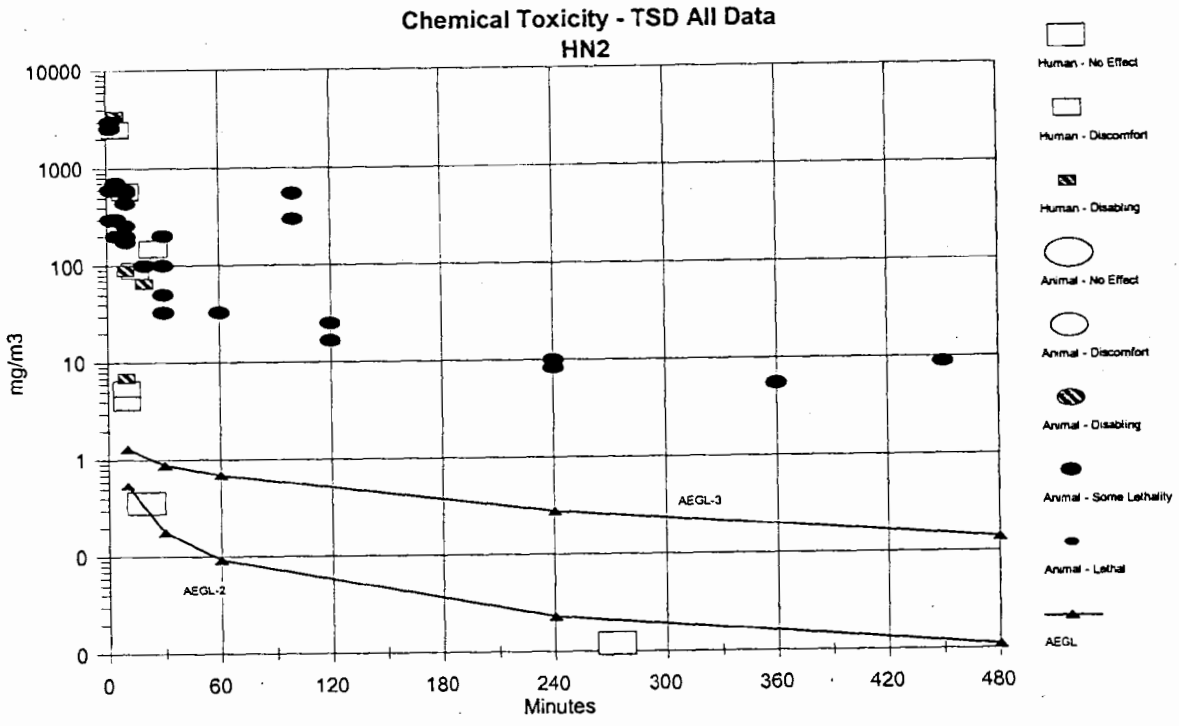
HN1
mg/m3
10000
1000
100
10
1
0
0
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
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100
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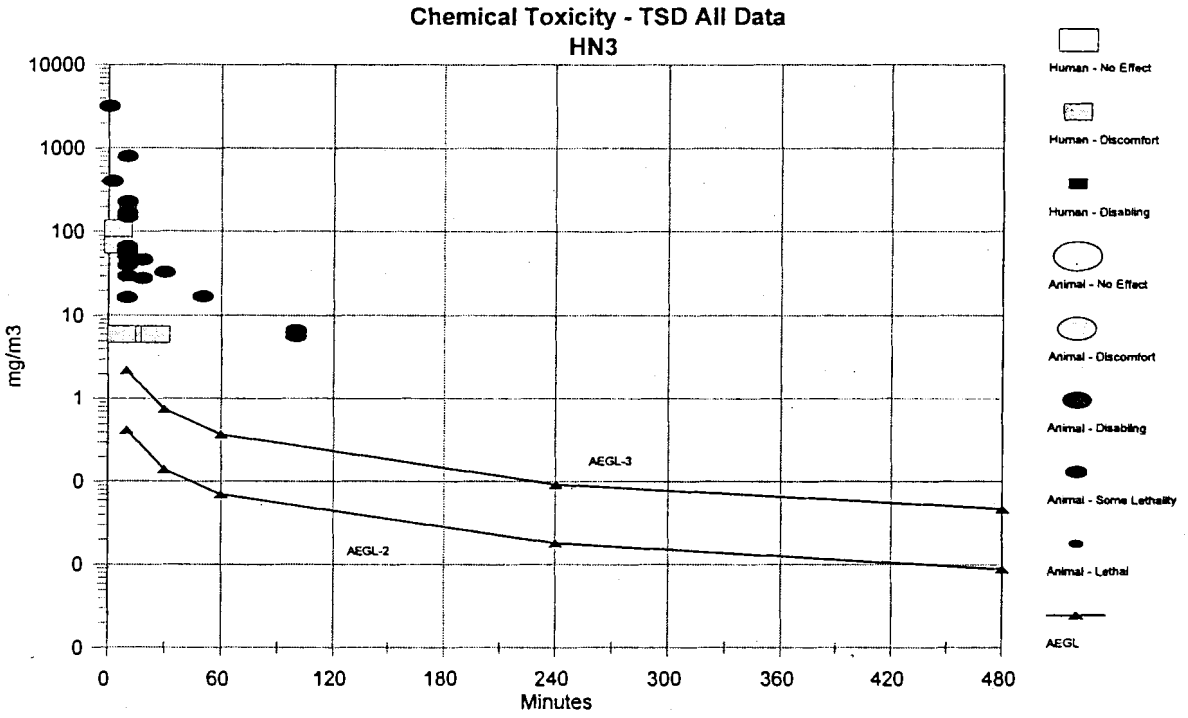
0
0
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL


Chemical Toxicity - TSD All Data
HN3
mg/m3
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1000
100
10
1
0
0
0
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

Application of Acute Exposure Guideline Levels

The Acute Exposure Level Guidelines have been developed primarily to provide guidance in situations were there can be a rare, typically accidental exposure to a particular chemical that can involve the general public. They, therefore, differ from PELs, TLV®s, WEEL®s, RELs or MAK values etc. in that they are based primarily on acute toxicology data and not subchronic or chronic data. The guidance therefore does not reflect the effects that could result from frequent exposure. Also, they are designed to protect the general population including the elderly and children, groups that are generally not considered in the development of workplace exposure levels. Users of the AEGL TSDs should first determine if there are legally enforceable standards that apply to the situation. Other organizations may also have recommended levels of exposure that more appropriately apply to the scenarios under evaluation.

It is however recognized that there may be an occasion where it may seem desirable to use these values for other exposure scenarios. In these cases, one should consult the technical support document. This document contains a comprehensive review of all identified acute toxicology data on the subject chemical and the basis for the development of the AEGL values. From this review one will have the information to determine the applicability of the AEGL to their particular situation.

Presentation given to NAC/AEGL Committee on September 23, 2004 regarding language on AEGL definition

Current main AEGL web page
http://www.epa.gov/oppt/aegl/

The Development of
Acute Exposure Guideline Levels (AEGLs)
A collaborative effort of the public and private sectors worldwide

Acute Exposure Guideline Levels, or AEGLs, describe the dangers to humans resulting from short-term exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both federal and local authorities, as well as private companies, deal with emergencies involving spills, or other accidental exposures.

SOP

The AEGL Standard Operating Procedures section "Purpose and Objectives of the AEGL Program and the NAC/AEGL Committee" (page 21) states:

> "The primary purpose of the AEGL program and the NAC/AEGL Committee is to develop guideline levels for once-in-a-lifetime, short-term exposures to airborne concentrations of acutely toxic, high-priority chemicals."

NEW DEFINITION FOR AEGL WEBSITE

Acute* Exposure Guideline Levels are intended to describe the risk to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both federal and local authorities, as well as private companies, deal with emergencies involving spills, or other catastrophic exposures.

*Definition = Acute exposures are single, non-repetitive exposures.

Changes adopted to AEGL definition after collecting formal vote on September 23, 2004

Acute* Exposure Guideline Levels, or AEGLs, are intended to describe the risk to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both ~~federal~~ national and local authorities, as well as private companies, deal with emergencies involving spills, or other catastrophic exposures.

*Definition = Acute exposures are single~~, non-repetitive~~ exposures for not more than 8 hrs.

↑ include

Guidelines for Use of PBPK Modeling in AEGL Value Development

The "White Paper"

1

Exposure → Target tissue → Response

Toxicokinetics
Pharmacokinetics
PBPK Models

Toxicodynamics
Pharmacodynamics
PBPD Models

2

Overview

- Until we can do all toxicology through computer simulation, we will have to extrapolate from animal studies
- Extrapolating using biological properties of the animals is the logical method
- We use UFs when we don't have an adequate biological description
- For some risk assessments, use of PBPK modeling is the default, use of UF is the backup

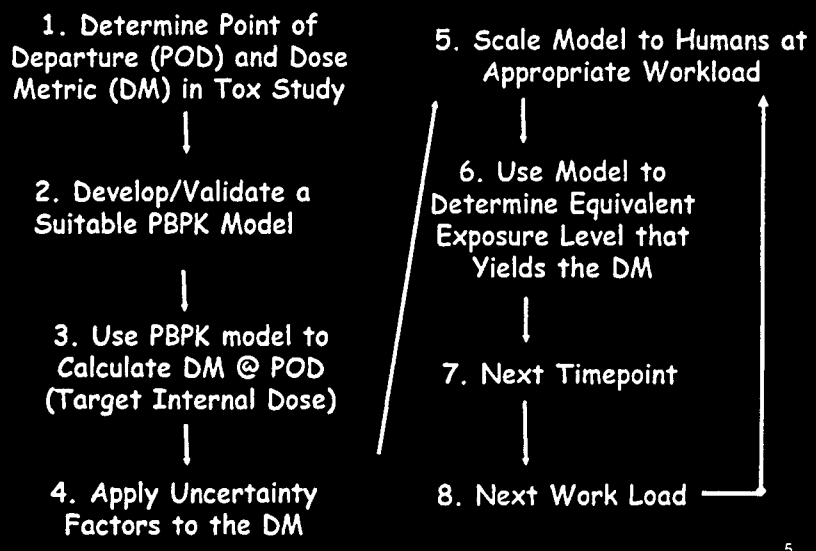
3

Principal Advantages

1. Improve the quality of the risk assessment
2. Avoid the difficult issue of setting UF
3. For chemicals that PBPK-AEGL is higher than UF-AEGL, avoid issue of "running into OELs"
4. For chemicals where PBPK-AEGL is lower than UF-AEGL, people are protected
5. Confidence in AEGL is higher
   - Extrapolate from animal study to human
   - Extrapolate from one duration to another
   - Take exercise into account

4

How Does it Work?



5

An Example-Toluene: Step 1

AEGL	Study	Species	NOAEL	Duration
AEGL1	Weight-of-Evidence	Human	200 ppm	8 Hours
AEGL2	Gamberale et al., 1972	Human	700 ppm	20 Minutes
AEGL3	Mullin and Krivanek, 1982	Rat	6250 ppm	2 Hours

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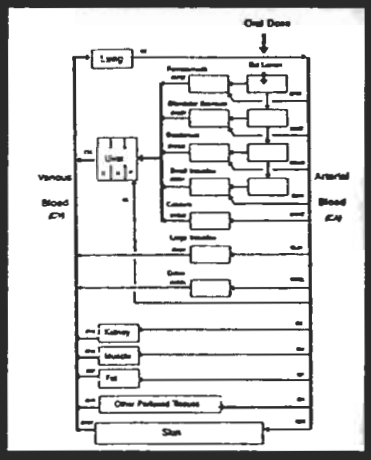
Step 2: Develop PBPK Model

Model Structure



Model Equations, e.g.

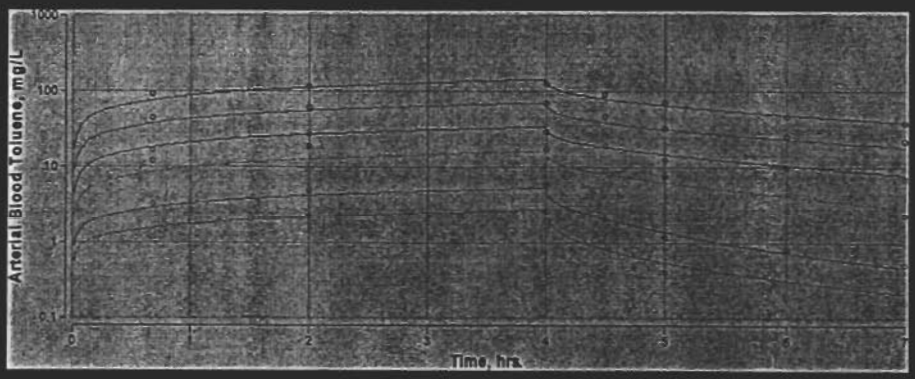
```
;Chemical in blood
  AB' = QP*(CI-CX) + QC*(CV-CA)
  INIT AB = 0
  CA = AB/VB
  CV = (QF*CVF + QR*CVR +
        QL*CVL + QS*CVS)/QC
```

Model Parameter Values, e.g.

VL = .05*BW
BW = 70 kg

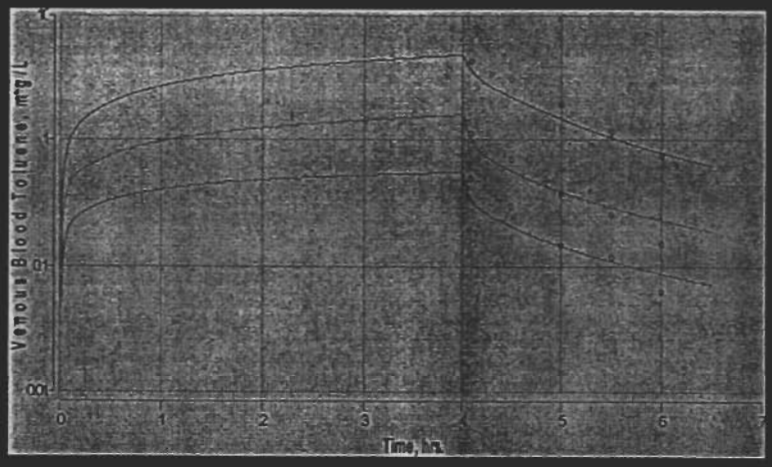
7

Step 2



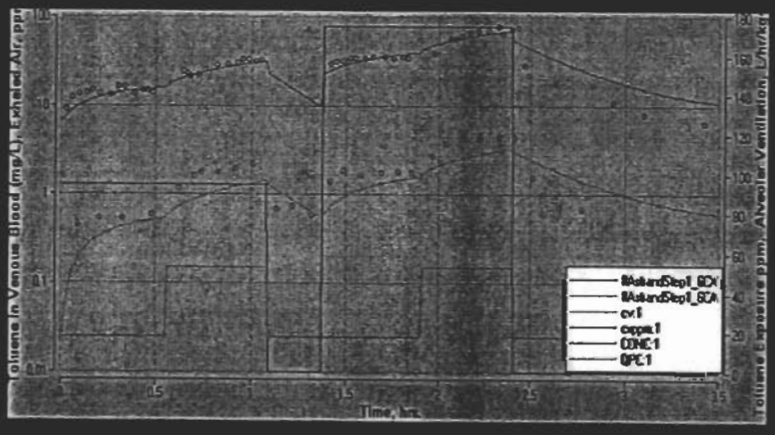
Model Development Adjust parameters to better fit data from Kishi et al. (1988). Exposed rats to toluene for 4 hours and measured toluene in venous blood during and after exposure.

8



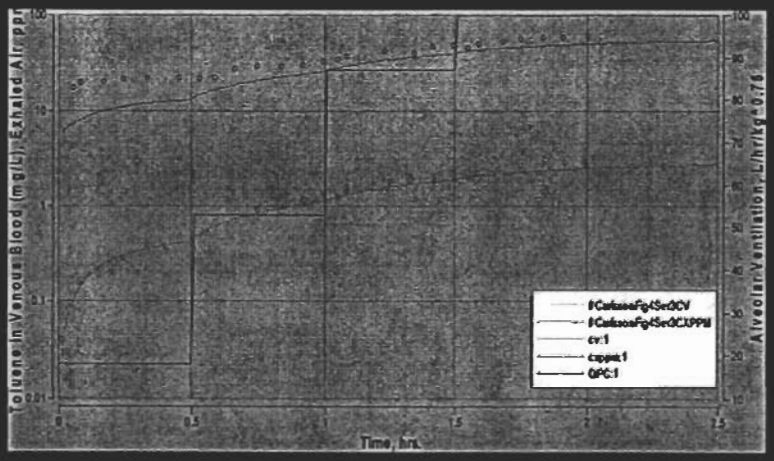
Model validation Check performance against other data sets. Blood data from Tardif et al. (1997)

9



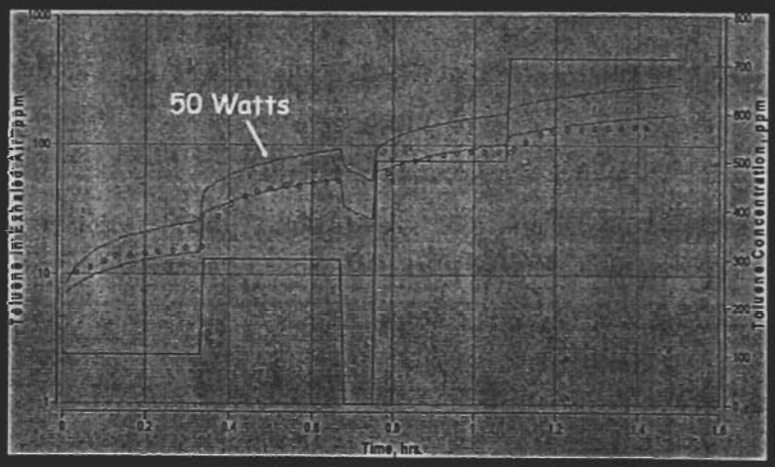
Validation of model performance in humans. Adjust model for human physiology and biochemistry. Test it against data from Astrand et al. (1972) at different concentrations and workloads.

10



Another validation. Data from Carlsson et al. (1982) at 80 ppm under four different workloads.

11



Data from Gamberale et al. (1972) at four different concentrations.

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AEGL-2 Calculations

Step 1: POD: Gamberale et al. (1972) 700 ppm exposure for 20 minutes in humans

DM: Toluene in venous blood

Step 3: DM @POD = 6.5 mg toluene/L

Step 4: Apply Uncertainty Factor (1)

Step 6: Use Human PBPK Model to determine Exposure Concentrations to yield 6.5 mg/L at each timepoint

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How Much Difference Does PBPK Make?

AEGL-1 Values Determined with PBPK and ten Berge, ppm

PBPK	10 min	30 min	1 hour	4 hour	8 hour
Rest	820	420	**330**	**230**	**(200)**
50W	**410**	**230**	160	110	100
75W	360	190	140	100	100
100W	320	170	120	100	90
Ten Berge	200	200	200	200	200

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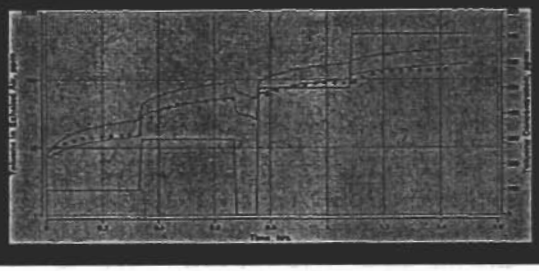
AEGL-2 Values Determined with PBPK and ten Berge, ppm

PBPK	10 min	30 min	1 hour	4 hour	8 hour
Rest	1580	780	**590**	**410**	**350**
50W	**810**	**430**	300	200	190
75W	700	370	260	190	180
100W	630	330	240	180	170
ten Berge	990	570	510	510	510



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AEGL-3 Values Determined with PBPK and ten Berge, ppm

PBPK	10 min	30 min	1 hour	4 hour	8 hour
Rest	12800	6070	**4490**	**2960**	**2440**
50W	**6670**	**3490**	2400	1530	**1430**
75W	5820	2980	2060	1440	**1370**
100W	5250	2690	1900	**1430**	**1350**
ten Berge	7.200	4.200	2,900	1.500	1.500

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Guidance Statements

"... relevant PBPK data can be used to reduce uncertainty in extrapolation and risk assessment" (NRC 1987).

addressing Community Emergency Exposure Levels:

"If PBPK models for calculating delivered dose and cross-species extrapolation have been developed, the pharmacokinetic information should be incorporated into the quantitative risk assessments" (NRC 1993).

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US EPA Guidance

"The optimal approach for extrapolating from one dose-duration response situation to another is the use of a physiologically based pharmacokinetic model (PBPK) model" (USEPA 2002).

Advocated PBPK modeling for setting AEGLs:

Krewski, et al. (2004)
Bruckner et al. (2004)
Simmons et al. (submitted)

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3 Stages of Consideration

- Initial determination of PBPK modeling feasibility
- In-depth determination of model adequacy
- Implementation

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Initial determination of PBPK modeling feasibility

- We don't want to waste resources

Do we think it will make a difference?

Are there existing model(s)?

Can the model "inform" the dose metric?

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In-depth determination of adequacy

- Can we modify existing models for species of interest?
- Are there sufficient data available to validate the model(s)
- Is the model validated in the exposure range of interest?
- Do we have workload validation?
- The basic difference between this and the initial determination of adequacy is that here, we need to do some modeling to find out

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Model Selection

- Was the model fully documented, in terms of equations and parameter values?
- Was the model validated? What kinds of data were used?
- Was the model published in the peer-reviewed literature?
- Is the model appropriate for AEGL development? Will it support computation of the dose metric?

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Data Selection

- Do the data involve exposures in the range of interest (i.e., likely range of AEGL values);
- Do the data provide multiple concentrations in one set of studies;
- Are data from timecourse studies rather than a single timepoint;
- Are there data for more than one tissue;
- Are the data collected in the species of interest;
- Are there PBPK model parameters for the experimental species;
- Were body weights reported;
- Are exposure conditions clearly defined;
- Is the route of exposure appropriate;
- Do the data relate to the dose metric;
- Are there data from more than one laboratory;
- Are there data for exercising humans.

23

Model Validation

- Are the deviations between simulations and experimental data large or small?
- Do the deviations have a systematic component, e.g., does the model consistently over- or under-predict portions of the data such as early timepoints, high exposures, etc?
- How does the magnitude of the deviations compare among the model undergoing validation and other models that have been used for risk assessment?
- How well does the model perform in the exposure range of interest?
- How rich were the animal and particularly the human data?

24

ATTACHMENT 24

OptiMetrics, Inc.

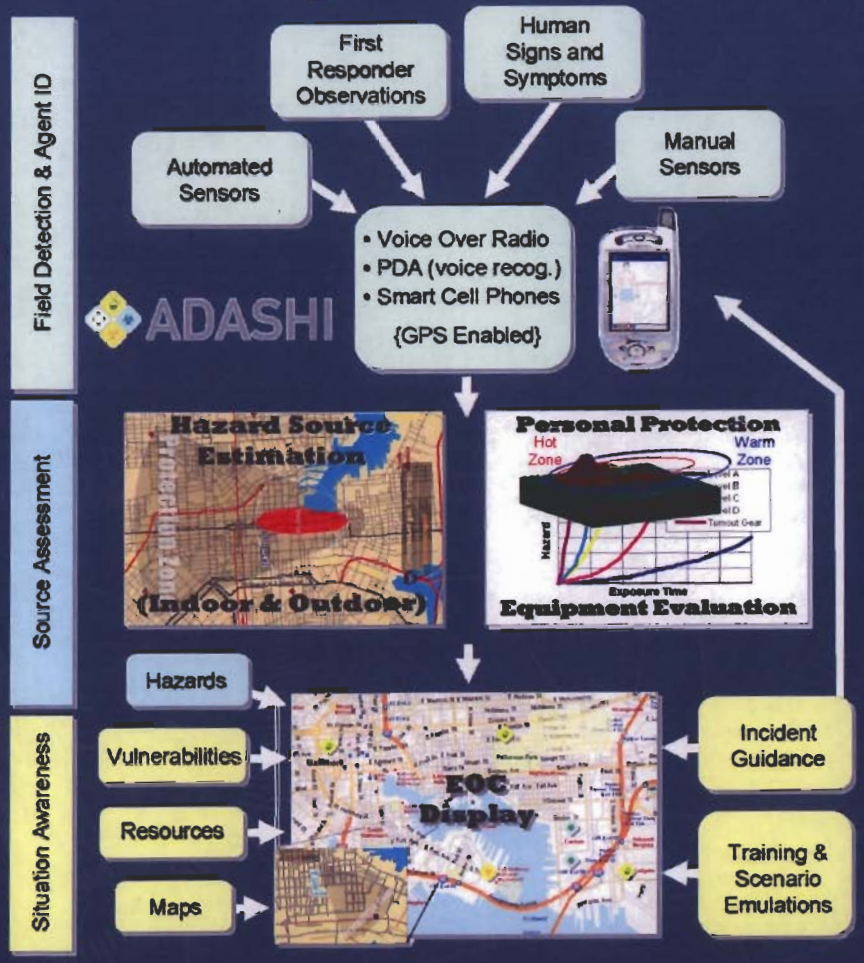
&

EDGEWOOD
CHEMICAL BIOLOGICAL CENTER
Since 1917–A Tradition of Solutions

ADASHI

Automated Decision-Aid System for Hazardous Incidents

ADASHI is ideally suited for integration with HPAC ITRANS



ADASHI's data acquisition, assessment, and mitigation decision aid.

- ADASHI technology licensed from ECBC
- Commercialization Funded by OptiMetrics
- Designed to handle everyday TICs and TIMs
- Designed to handle infrequent WMD events
- Currently uses ALOHA and ERG for Hazard Area Estimation
- Requires no training

Evolution of ADASHI Products

- ADASHI First Response
  - Laptop Application for On-Scene Situation Assessment
  - Currently Available as Commercial Product for First Responders
- ADASHI Owl
  - Palmtop or Cell Phone Application for Individual Responder Situation Assessment, Data Collection and GPS Location Sensing
  - Initial Commercial Product Release Planned for Late 04
- ADASHI Eagle
  - Desktop or Laptop Application for Remote or On-Scene Situation Assessment, Response Guidance and Command, Control and Communications
  - Initial Commercial Product Release Planned for Summer 05

ADASHI Product Line

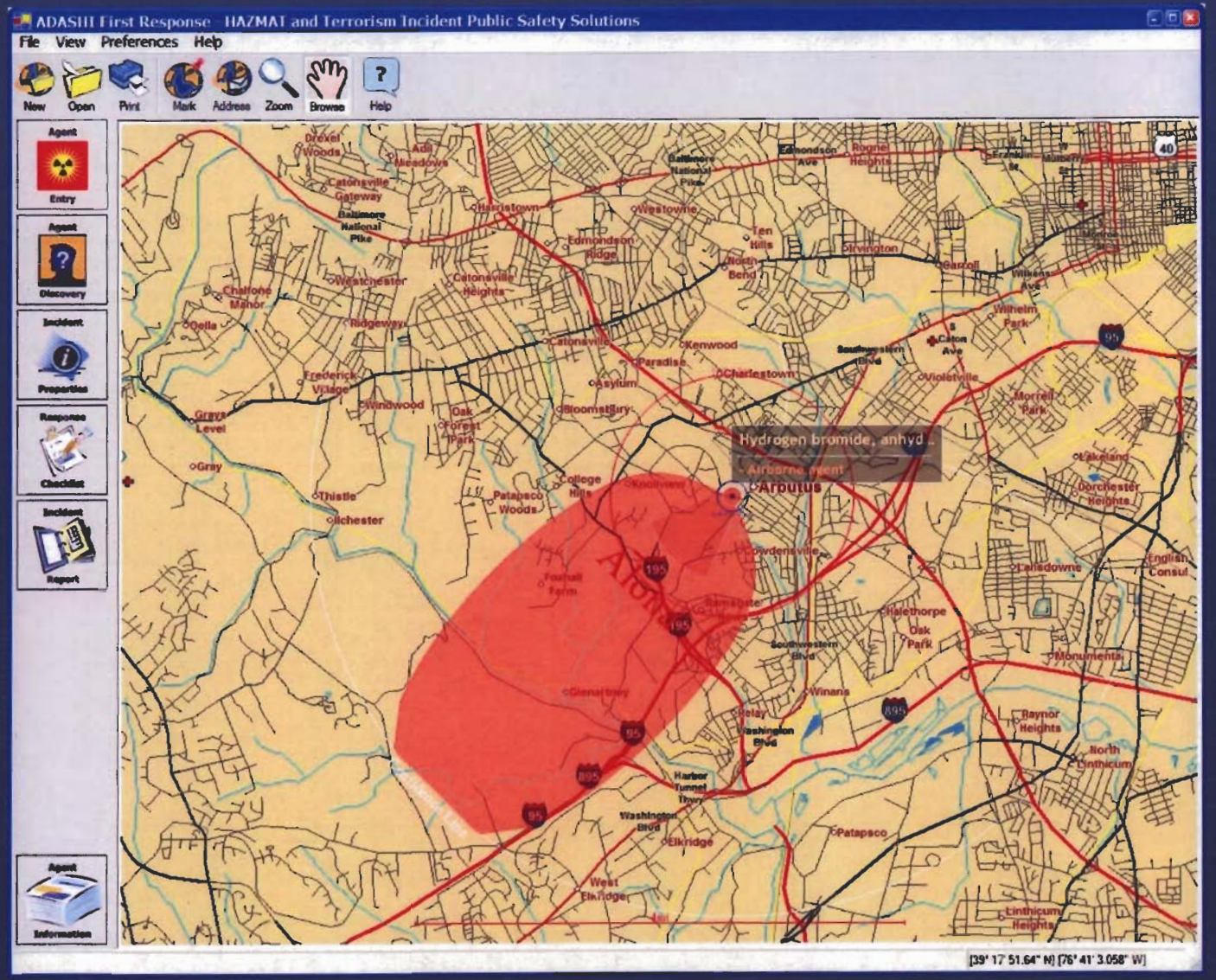
Feature	First Response	ADASHI Owl	ADASHI Eagle
Source Identification (Chemical, Biological, Radiological, & Nuclear)			
Rail cars, trailers, drums, and tank configurations (HAZMAT Transport - HT)	✓	✓ (HT)	✓ (HT)
Human and observed signs and symptoms, manual, and automated detectors		✓	✓
False alarm and confounding agent identification		✓	✓
PDA portable data entry within Level A Suit with GPS tracking		✓	✓
Multiple source identification and interaction analysis		✓	✓
Automated worst case scenario generation	✓	✓	✓
Automated meteorological data acquisition	✓	✓	✓
Street map and hazard visualization (ESRI and other mapping programs)	✓	✓	✓
ERG 2000 isolation, fire, and spill safe distances	✓	✓	✓
Outdoor atmospheric dispersion modeling	✓	✓	✓
Vulnerability, hazards, and resource tracking with full scheduling capabilities		✓	✓
Equipment inventories (detector, PPE, decontamination)		✓	✓
Guidance on detection, public safety, first aid, PPE, decon., and communication		✓	✓
Microsoft's active directory security integration and responder role assignments			✓
Communication (military/civilian, messenger, video, and action tracking/logging)			✓

Immediate Incident Guidance

Customizable Guidance Checklists & SOPs →

Formal & Action Reports →

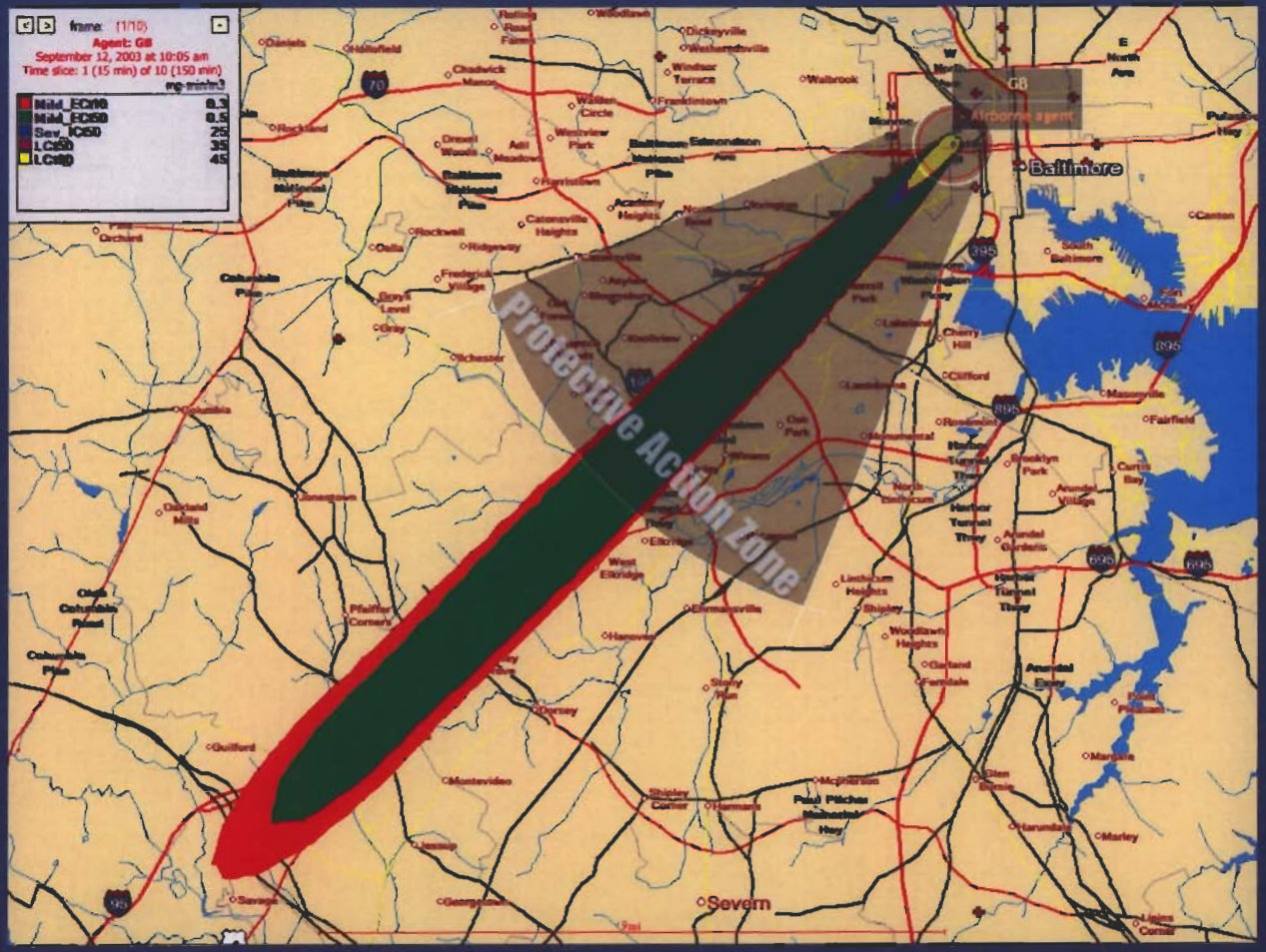
Agent Information →



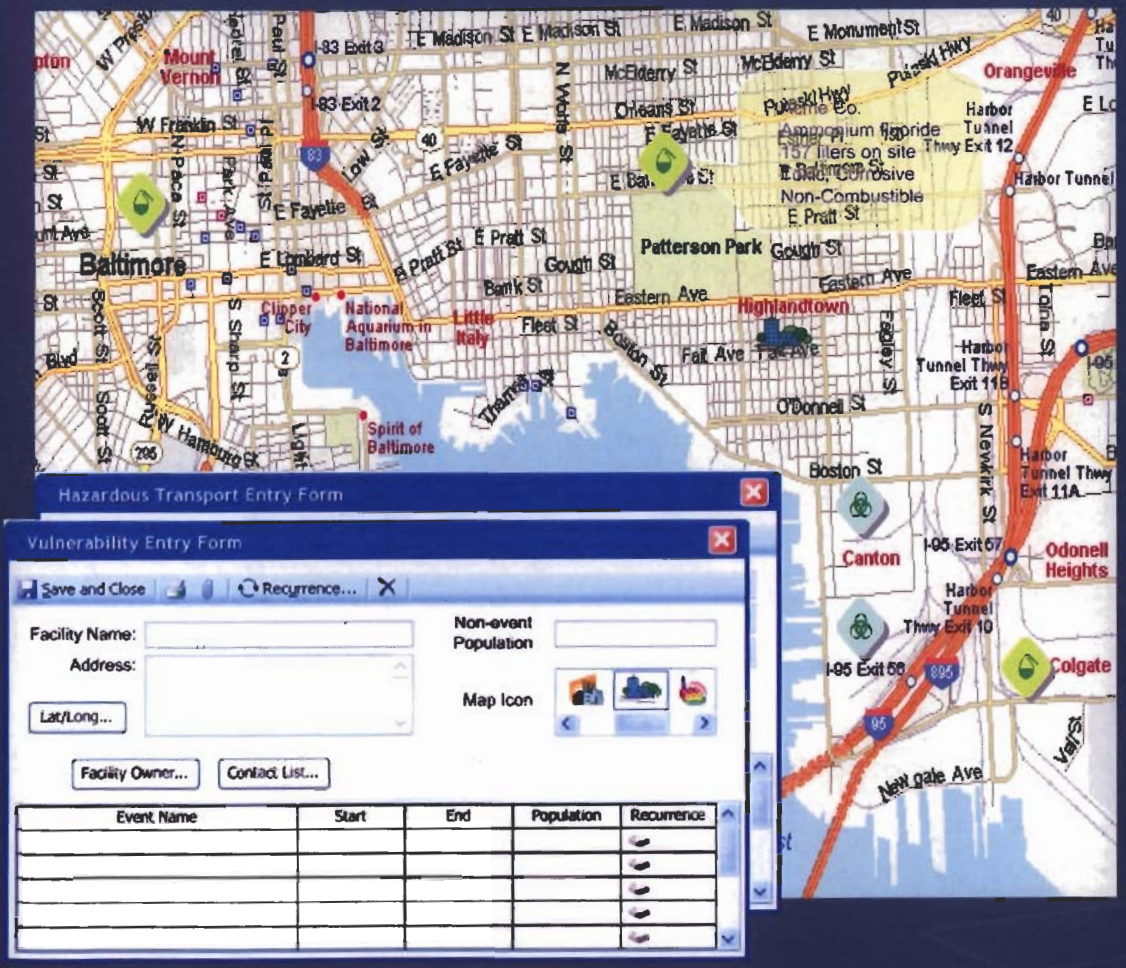
ALOHA vs. HPAC

ALOHA	HPAC
No terrain steering	Complex terrain inclusion and model effects
Static 2-dimentional hazard analysis	Dynamic 3 (4)-dimensional hazard analysis
Static single sources	Static and moving multiple sources
Static weather model (wind > 3mph)	4-dimentional robust dynamic weather inclusion
Chemical agents only	Nuclear, Chemical, Biological, and Radiological
No fire modeling	Fireball and jet fire models
No energetic event modeling	Blast, explosive, and nuclear models

ADASHI as an Interface to HPAC



Resources, Vulnerabilities, and Hazards -> ITRANS



Please enter the agent name:

- ERG Model
- ALOHA Model

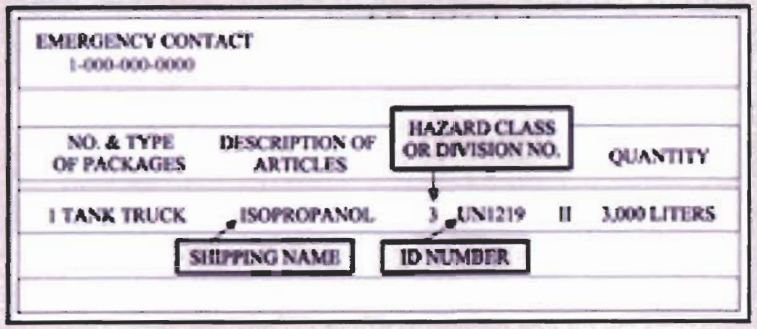
Rate your certainty in your selection

Not Certain ——— Very Certain

Done | Cancel

Agent names and IDs can be found on placards (possibly attached to intermodal containers) and shipping documents.

Sample Placards



Sample Shipping Document

Human Signs and Symptoms

Select Body Section

Patient Name

1b12d926-c95f-4407-9ba2-b01b6

Number of Patients

1

Cancel

Done

Torso

Cardiovascular

Respiratory

Gastrointestinal

Muscular

Skin

Respiratory.Observations

Back

Coughing

Breathing Difficulties

Change in Voice Quality

Normal

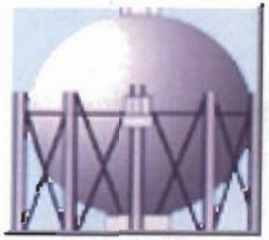
Current Symptoms	Onset	Intensity

TankTypeSelection

Please select the type of tank or drum:

Low Pressure
Cylinder Shape

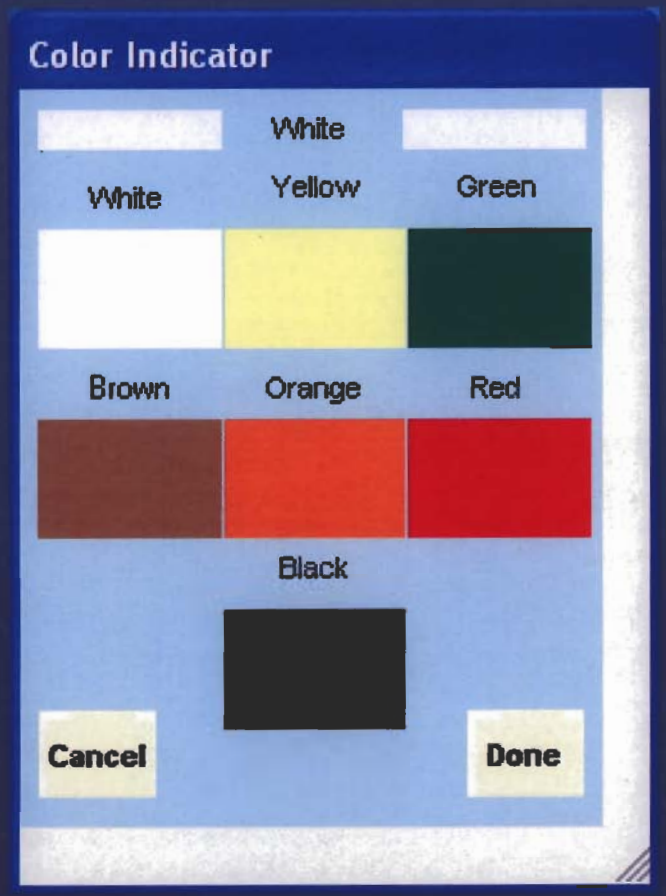
High Pressure
Cylinder Shape

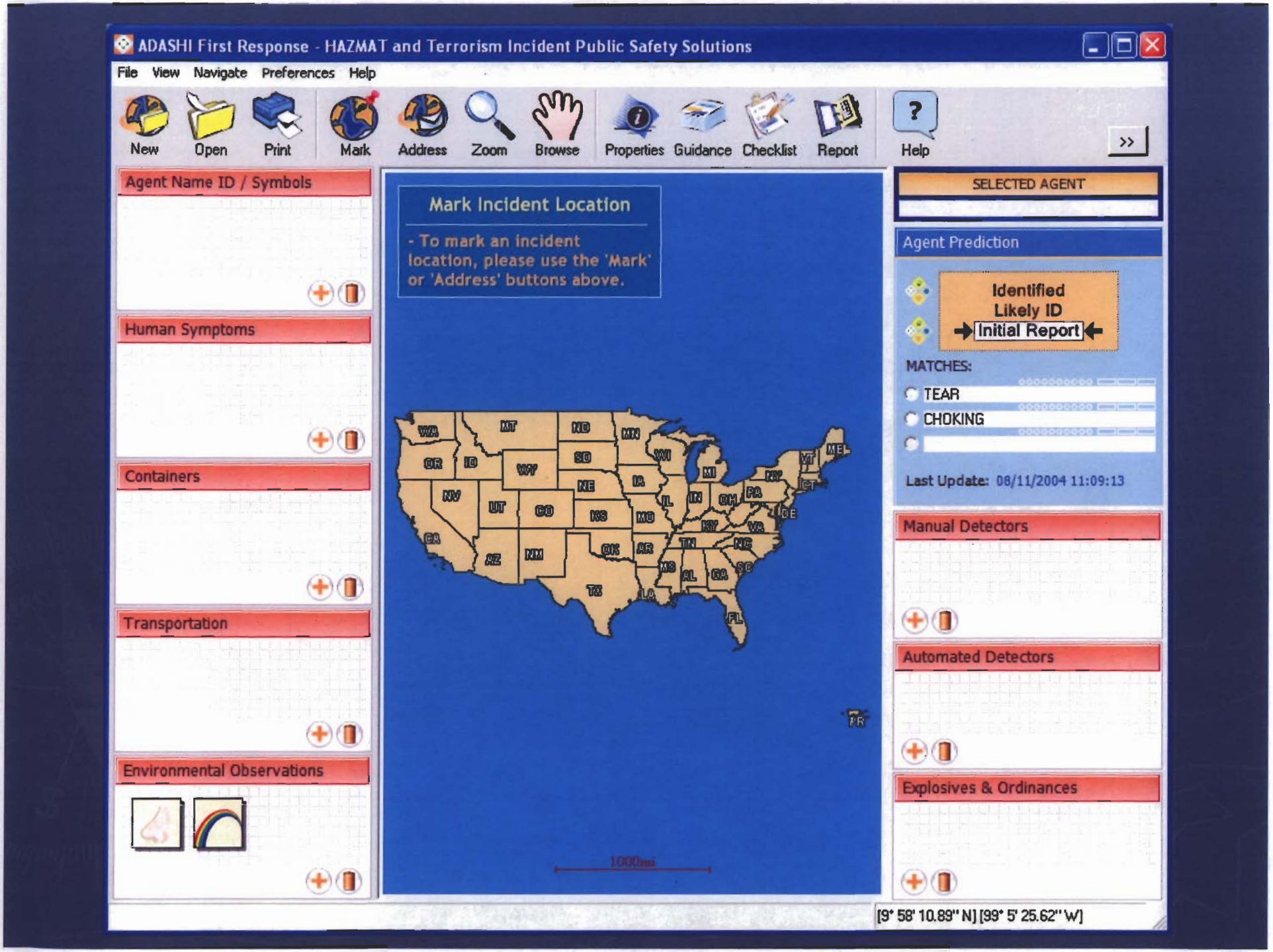


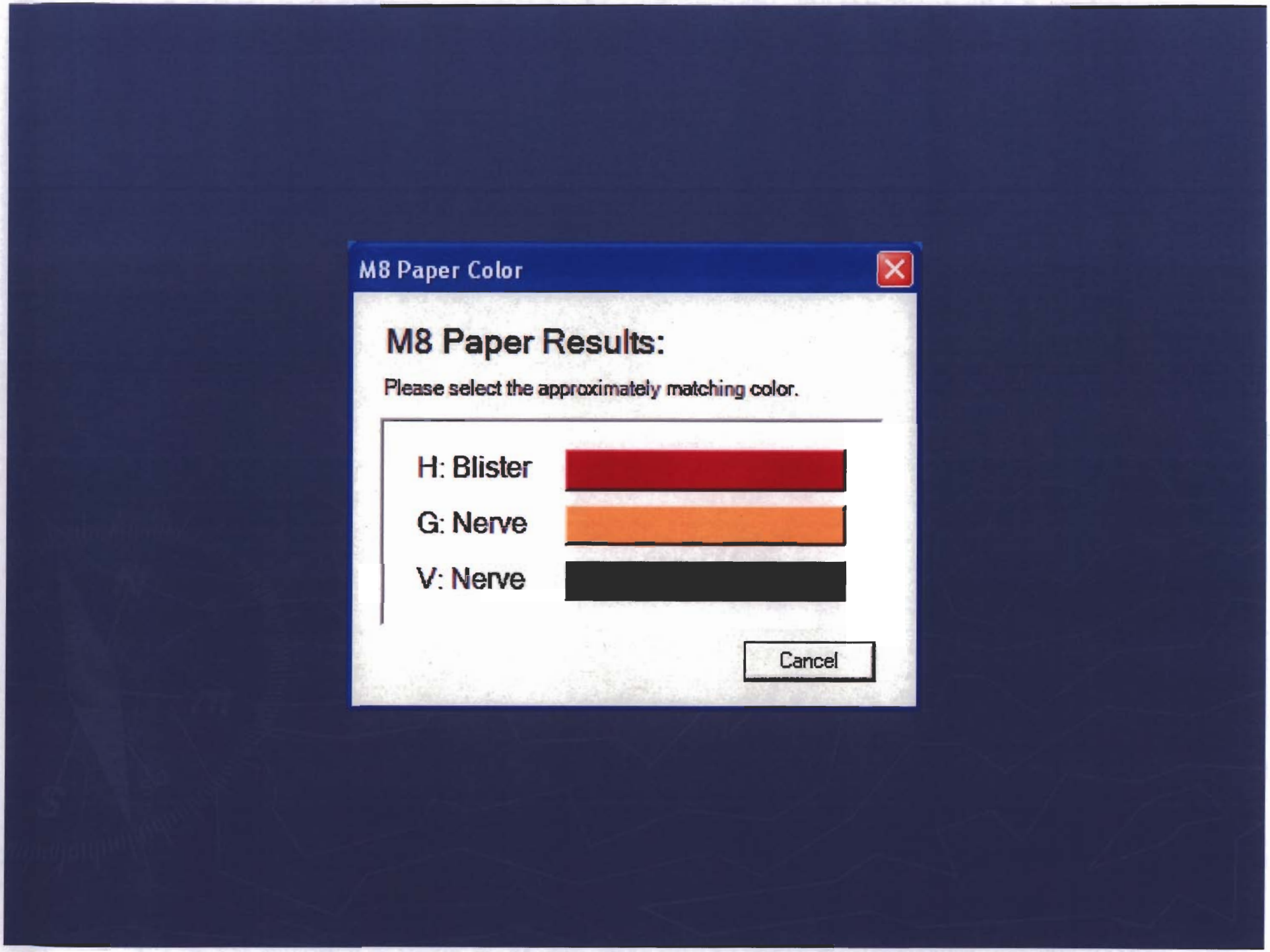
Spherical

Cancel


Odor Indicator
Odors
Odor
New Mown Hay
Chlorinated Swimming Pool
Peppers
No Odor
End of List
Scroll
Cancel
Done


Color Indicator
White
White
Yellow
Green
Brown
Orange
Red
Black
Cancel
Done

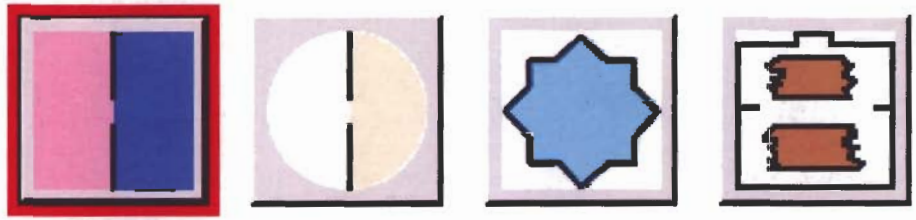

ADASHI First Response - HAZMAT and Terrorism Incident Public Safety Solutions
File View Navigate Preferences Help
New Open Print Mark Address Zoom Browse Properties Guidance Checklist Report Help
Agent Name ID / Symbols
Human Symptoms
Containers
Transportation
Environmental Observations
Mark Incident Location
- To mark an incident location, please use the 'Mark' or 'Address' buttons above.
SELECTED AGENT
Agent Prediction
Identified
Likely ID
Initial Report
MATCHES:
TEAR
CHOKING
Last Update: 08/11/2004 11:09:13
Manual Detectors
Automated Detectors
Explosives & Ordinances
[9° 58' 10.89" N] [99° 5' 25.62" W]


M8 Paper Color
M8 Paper Results:
Please select the approximately matching color.
H: Blister
G: Nerve
V: Nerve
Cancel

M256KitSelection

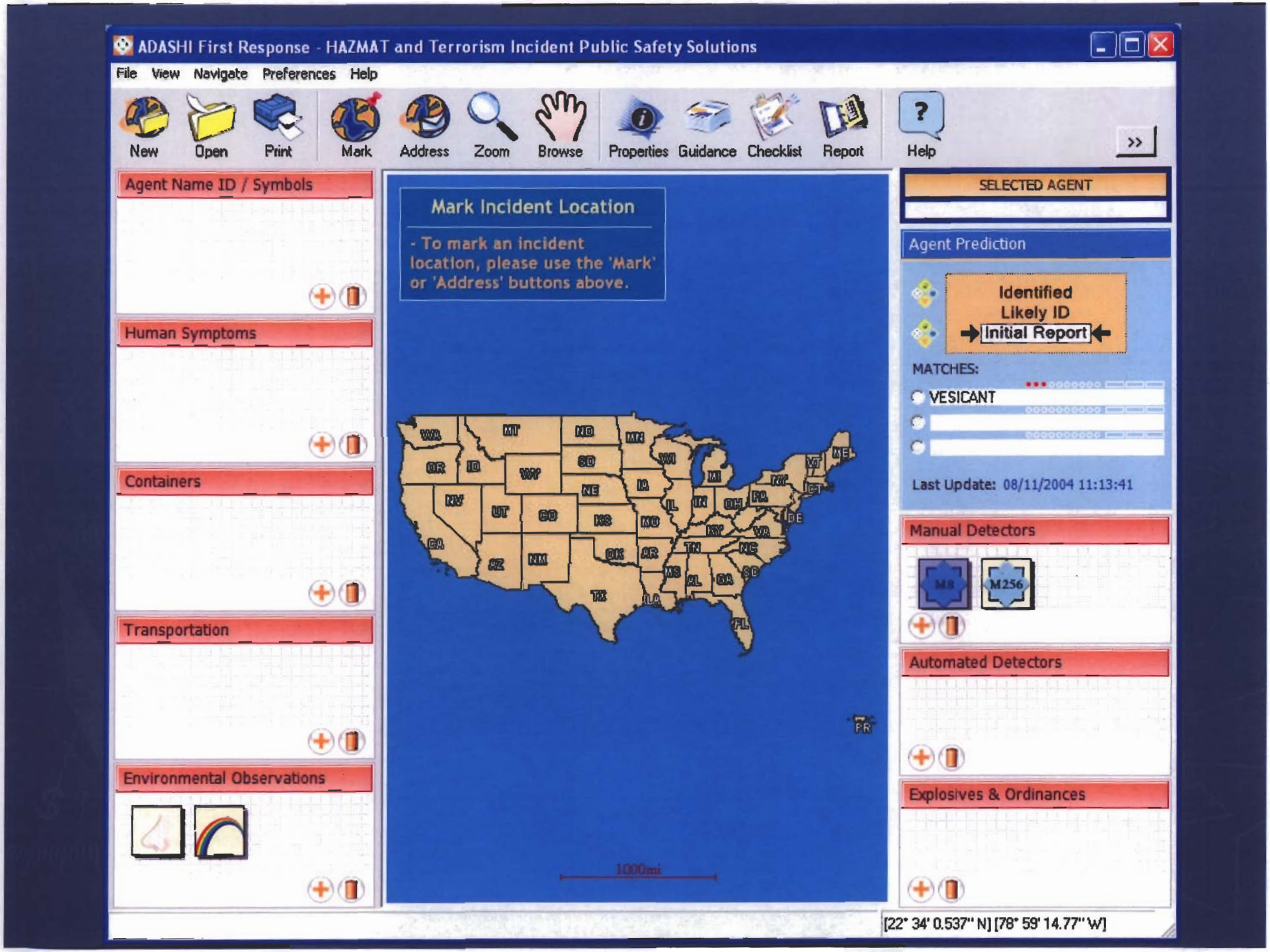
M256 Kit Results

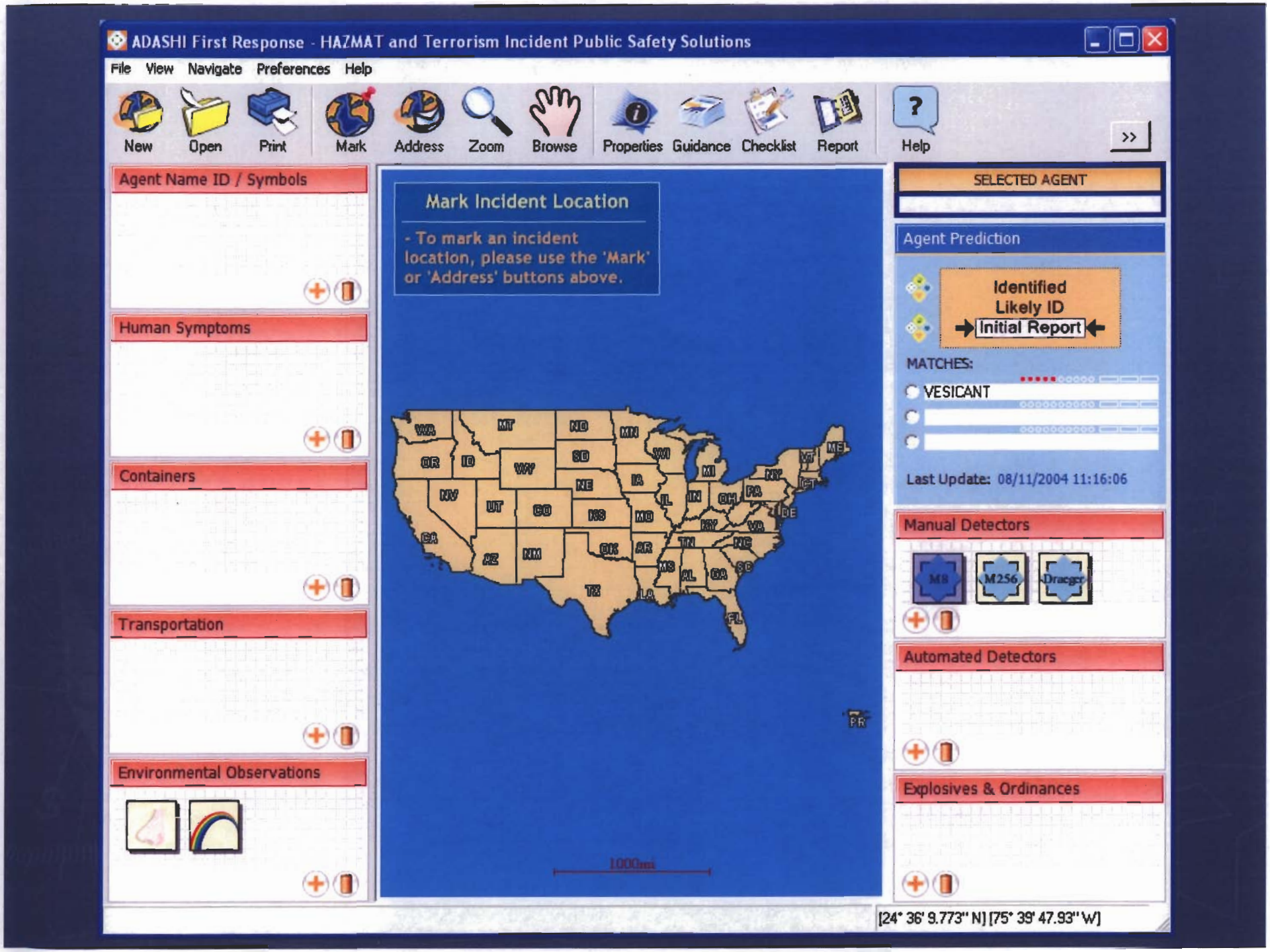
Please select the results of testing with the M256 kit. Red outline indicates the agent is present.

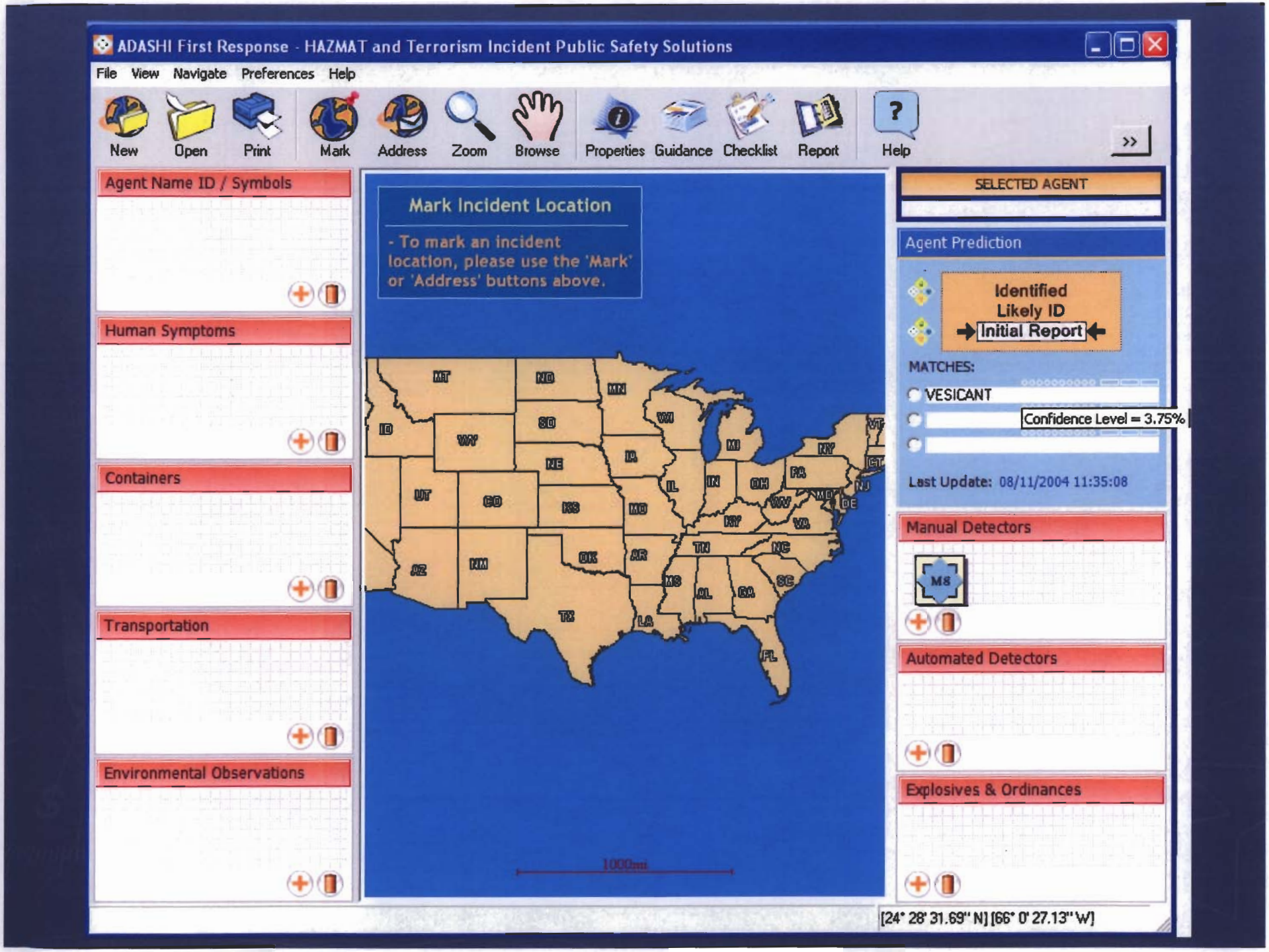


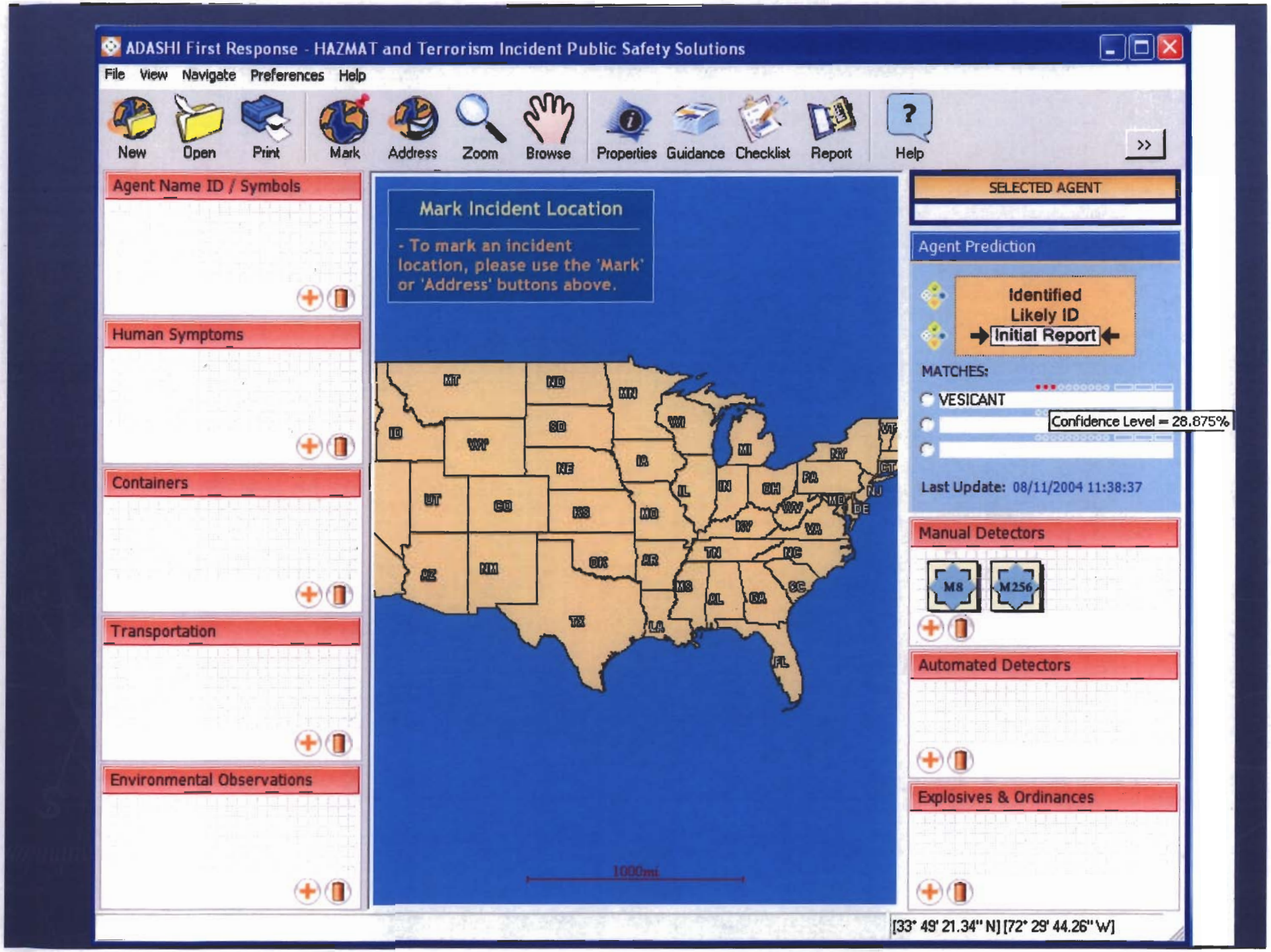
Blister	Blood	Nerve	Lewisite
(present)	(absent)	(absent)	(absent)

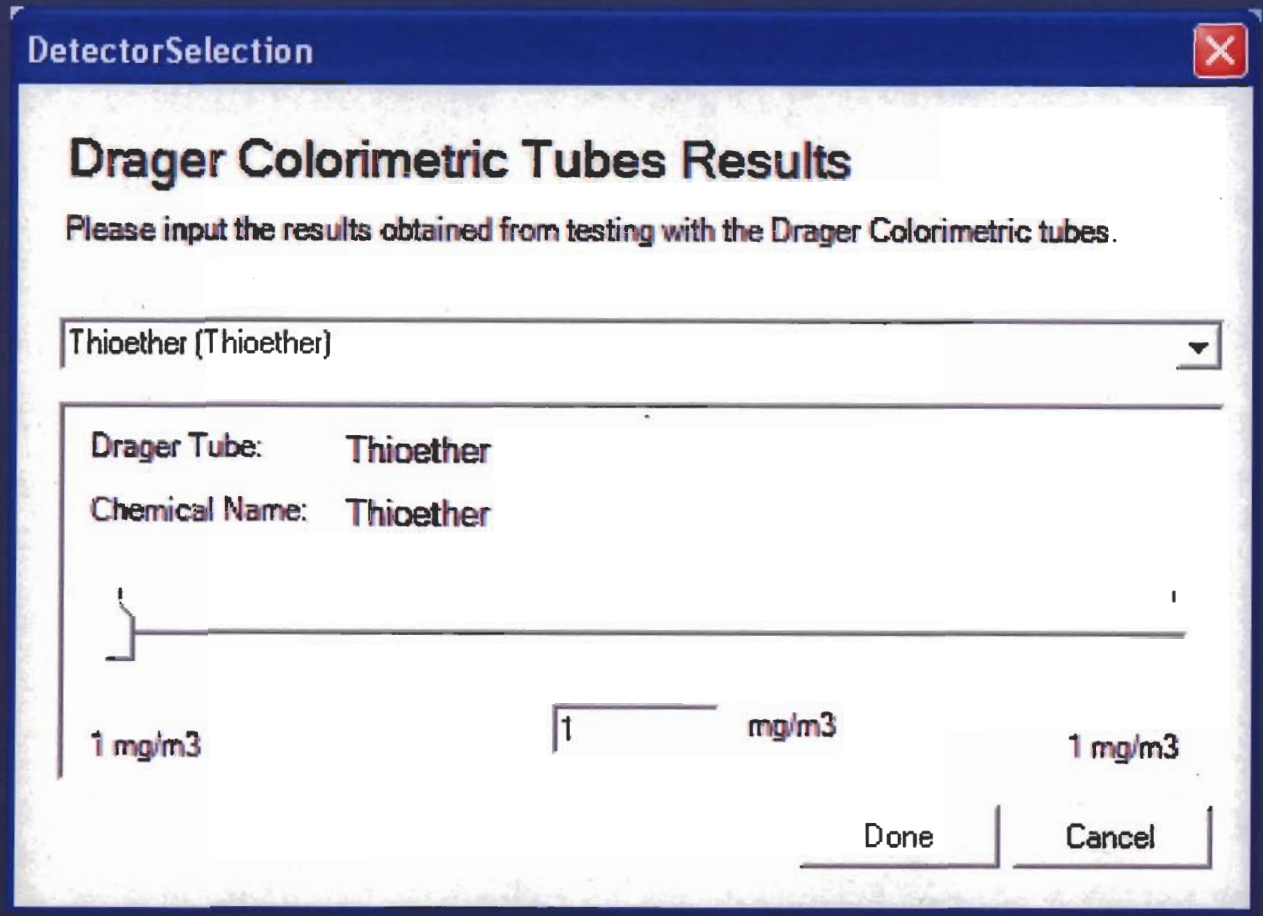
Done Cancel

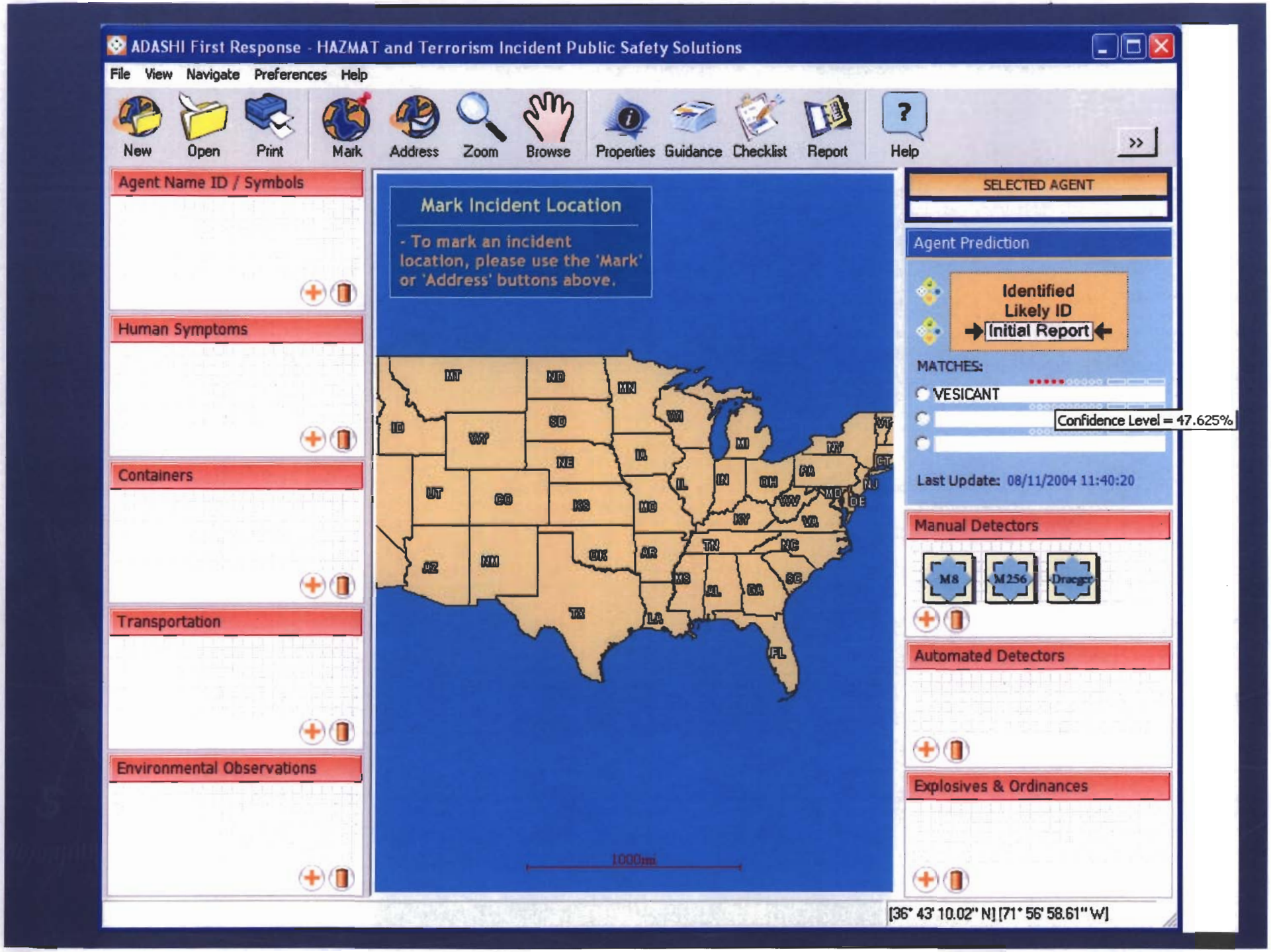

ADASHI First Response - HAZMAT and Terrorism Incident Public Safety Solutions
File View Navigate Preferences Help
New Open Print Mark Address Zoom Browse Properties Guidance Checklist Report Help
Agent Name ID / Symbols
Human Symptoms
Containers
Transportation
Environmental Observations
Mark Incident Location
- To mark an incident location, please use the 'Mark' or 'Address' buttons above.
1000mi
SELECTED AGENT
Agent Prediction
Identified
Likely ID
Initial Report
MATCHES:
VESICANT
Last Update: 08/11/2004 11:13:41
Manual Detectors
M8
M256
Automated Detectors
Explosives & Ordinances
[22° 34' 0.537" N] [78° 59' 14.77" W]

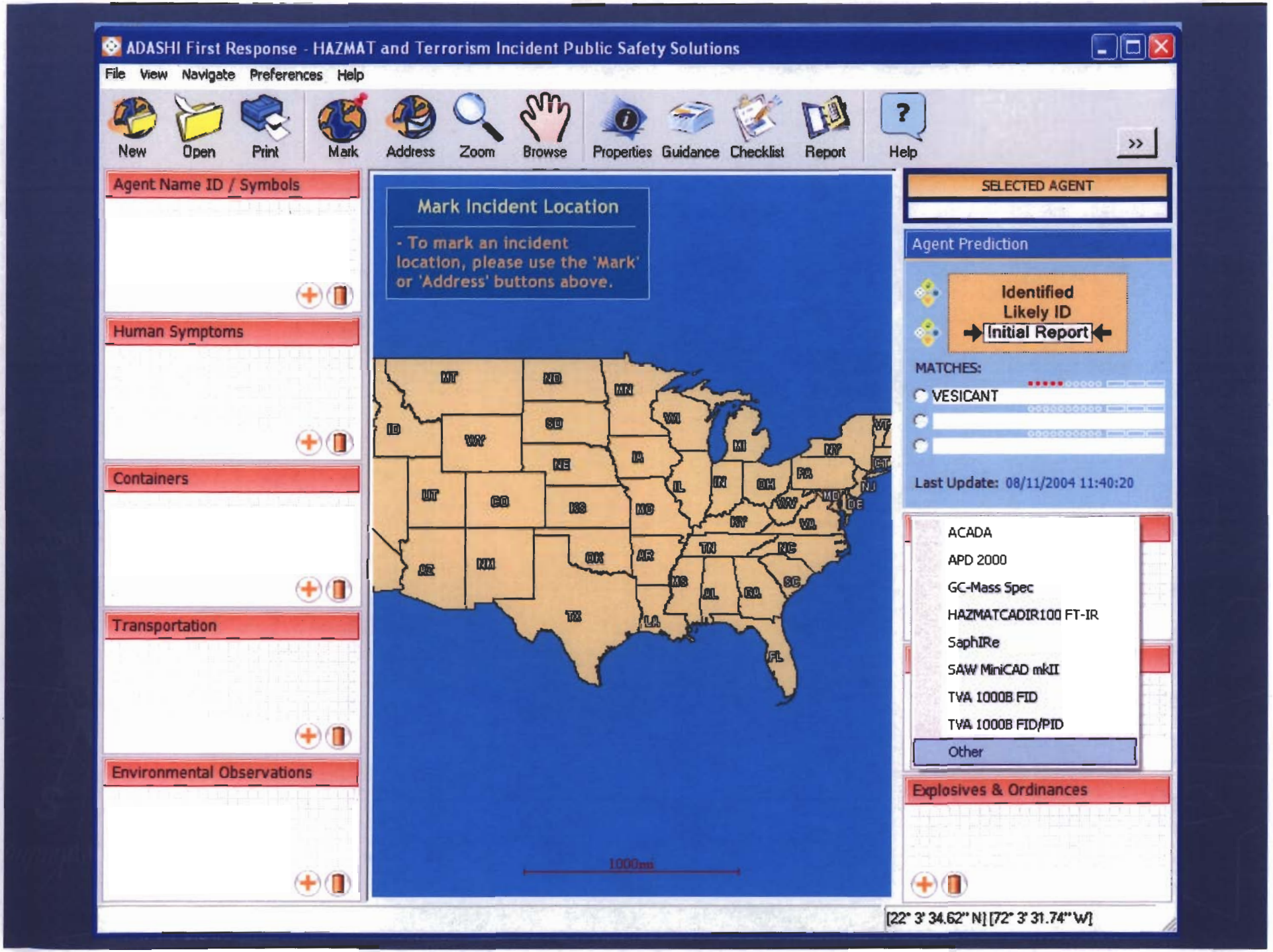

ADASHI First Response - HAZMAT and Terrorism Incident Public Safety Solutions
File View Navigate Preferences Help
New Open Print Mark Address Zoom Browse Properties Guidance Checklist Report Help
Agent Name ID / Symbols
Human Symptoms
Containers
Transportation
Environmental Observations
Mark Incident Location
- To mark an incident location, please use the 'Mark' or 'Address' buttons above.
SELECTED AGENT
Agent Prediction
Identified
Likely ID
Initial Report
MATCHES:
VESICANT
Last Update: 08/11/2004 11:16:06
Manual Detectors
M8
M256
Drager
Automated Detectors
Explosives & Ordinances
[24° 36' 9.773" N] [75° 39' 47.93" W]


ADASHI First Response - HAZMAT and Terrorism Incident Public Safety Solutions
File View Navigate Preferences Help
New Open Print Mark Address Zoom Browse Properties Guidance Checklist Report Help
Agent Name ID / Symbols
Human Symptoms
Containers
Transportation
Environmental Observations
Mark Incident Location
- To mark an incident location, please use the 'Mark' or 'Address' buttons above.
1000mi
SELECTED AGENT
Agent Prediction
Identified
Likely ID
Initial Report
MATCHES:
VESICANT
Confidence Level = 3.75%
Last Update: 08/11/2004 11:35:08
Manual Detectors
M8
Automated Detectors
Explosives & Ordinances
[24° 28' 31.69" N] [66° 0' 27.13" W]


ADASHI First Response - HAZMAT and Terrorism Incident Public Safety Solutions
File View Navigate Preferences Help
New Open Print Mark Address Zoom Browse Properties Guidance Checklist Report Help
Agent Name ID / Symbols
Human Symptoms
Containers
Transportation
Environmental Observations
Mark Incident Location
- To mark an incident location, please use the 'Mark' or 'Address' buttons above.
1000mi
SELECTED AGENT
Agent Prediction
Identified
Likely ID
Initial Report
MATCHES:
VESICANT
Confidence Level = 28.875%
Last Update: 08/11/2004 11:38:37
Manual Detectors
M8
M256
Automated Detectors
Explosives & Ordinances
[33° 49' 21.34" N] [72° 29' 44.26" W]

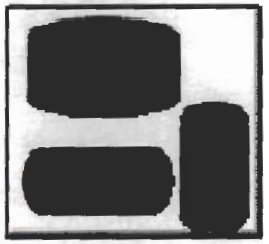

DetectorSelection
Drager Colorimetric Tubes Results
Please input the results obtained from testing with the Drager Colorimetric tubes.
Thioether (Thioether)
Drager Tube: Thioether
Chemical Name: Thioether
1 mg/m3
1
mg/m3
1 mg/m3
Done
Cancel


ADASHI First Response - HAZMAT and Terrorism Incident Public Safety Solutions
File View Navigate Preferences Help
New Open Print Mark Address Zoom Browse Properties Guidance Checklist Report Help
Agent Name ID / Symbols
Human Symptoms
Containers
Transportation
Environmental Observations
Mark Incident Location
- To mark an incident location, please use the 'Mark' or 'Address' buttons above.
1000mi
SELECTED AGENT
Agent Prediction
Identified
Likely ID
Initial Report
MATCHES:
VESICANT
Confidence Level = 47.625%
Last Update: 08/11/2004 11:40:20
Manual Detectors
M8
M256
Dragger
Automated Detectors
Explosives & Ordinances
[36° 43' 10.02" N] [71° 56' 58.61" W]

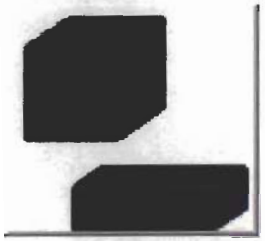

ADASHI First Response - HAZMAT and Terrorism Incident Public Safety Solutions
File View Navigate Preferences Help
New Open Print Mark Address Zoom Browse Properties Guidance Checklist Report Help
Agent Name ID / Symbols
Human Symptoms
Containers
Transportation
Environmental Observations
Mark Incident Location
- To mark an incident location, please use the 'Mark' or 'Address' buttons above.
1000mi
SELECTED AGENT
Agent Prediction
Identified
Likely ID
Initial Report
MATCHES:
VESICANT
Last Update: 08/11/2004 11:40:20
ACADA
APD 2000
GC-Mass Spec
HAZMATCADIR100 FT-IR
SaphIRe
SAW MiniCAD mkII
TVA 1000B FID
TVA 1000B FID/PID
Other
Explosives & Ordinances
[22° 3' 34.62" N] [72° 3' 31.74" W]

DevicesTypeSelection

Please select a device or ordinance:



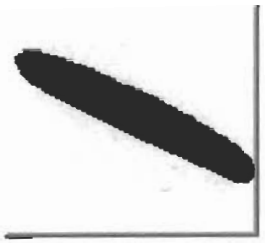
Canister



Box

Ball

Grenade



Cigar

Other Ordinances

Cancel