

MEMORANDUM

Date: August 12, 1999

Subject: Phosphine Gas: Response to Comments from the Phosphine Coalition.
DP Barcode: D258581, PC Code: 066501

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Introduction

On behalf of the Phosphine Coalition, Sciences International, Inc. and Technology Sciences Group, Inc. have commented on the proposed risk mitigation measures. Both parties have proposed distinctly different ways of raising the maximum permissible exposure level for phosphine gas from the current level of 0.03 ppm. This level was derived by dividing a 90-day rat NOAEL of 3 ppm by an interspecies uncertainty factor (UF) of 10 and an intraspecies UF of 10. This memorandum addresses the Coalition's recommendations, beginning with those from Sciences International, Inc., and then those from Technology Sciences Group, Inc.

Recommendations from Sciences International, Inc.

On April 15, 1999, staff from the Health Effects Division and the Reregistration Division met with the Phosphine Coalition. Speaking for the Coalition, Elizabeth Andersen of Sciences International suggested several approaches to eliminating the 10-fold interspecies uncertainty factor (UF). These included, a.) a comparison of phosphine toxicity in a variety of animals, b.) RGDR dosimetry adjustment, and c.) categorical regression and benchmark dosing to derive Acute Reference Exposure (ARE) values. Of these, the RGDR dosimetry adjustment appeared to be the only option that might allow the interspecies UF to be reduced. The Coalition was told that there is no possibility of eliminating the UF altogether. HED agreed to consider a full documentation of their proposals.

Sciences International, Inc. has submitted an *Interim Status Report: Phosphine Toxicity Review* for Agency review (dated July 1999, attached), but it lacks the supporting data and procedures that HED had requested. Instead, it contains the same information that was verbally conveyed at the April meeting. The recommendations are too vague for meaningful comment beyond what was already offered at the meeting.

The Coalition is contesting the use of an interspecies uncertainty factor (UF) of 10. If the interspecies UF were eliminated, the regulatory values would increase ten-fold. They have offered three justifications for doing this.

Interspecies UF of 1

Issue: It is the Coalition's opinion that there is strong scientific evidence that the 10-fold interspecies UF is unnecessarily conservative, and that an interspecies UF of 1 is supported by the available data.

Response: There is no precedent for using an UF of 1 when establishing a reference concentration (RfC) or an inhalation regulatory value in the Health Effects Division. The only time an interspecies UF is not applicable is when human data are used. The available data do not support deviating from Agency policy, and the Coalition did not provide any new data.

A Comparison of Lethal Concentrations

Issue: The Coalition supplied LC₅₀ values for rats and frogs, and LC₁₀₀ values for rats, cats, rabbits, guinea pigs, turkeys, and hens. The fact that toxicity is fairly constant across species proves that an interspecies UF is not necessary.

Response: The lethal concentration comparison in Table 1 fails to prove why the interspecies UF should be reduced due to a lack of information and irrelevant comparisons:

1. "Exposure times" ranged from 0.6 to 17.8 hours. Since some of the exposure times were ranges (e.g. 1.2 - 17.8 hours for cats), they probably were not exposure times, but rather time-to-effect (i.e. time-to-death).

2. It is unreasonable to compare concentrations that kill half (LC_{50}) versus all (LC_{100}) of the animals.
3. OPP bases risk assessments on NOAELs, not lethal doses/concentrations. Threshold toxicity among species would have been a more relevant comparison than death.
4. Exposures were in "ppm-hours," which was not defined. Presumably, ppm-hours is the ppm concentration divided by the length of exposure (or time-to-effect). If so, this is stretching Haber's Law beyond the limit of credibility.
5. There is no way of knowing whether the exposure concentrations were nominal or analytical.
6. Table 1 compares mammals, birds, and amphibians. This is not a fair comparison because of significant pharmacokinetic and pharmacodynamic differences between these classes. For example, frogs are cold-blooded, and their skin may be permeable to phosphine gas.
7. The main purpose of the interspecies UF is to account for the metabolic differences between laboratory animals, which are small, and humans, which are large. All of the animals in Table 1 are small except for turkeys (a non-mammal). It comes as no surprise that lethal concentrations for small animals would be similar. The Coalition's contention can only be substantiated if it compares toxicity (not death) for a small mammal, such as rats, and a large mammal, such as dogs.

Regional Gas Deposited Dose (RGDR)

Issue: Based on an analysis of rat and mouse studies completed for the purpose of conducting a categorical regression, phosphine is a category 2 gas. Calculated RGDRs varied between 0.91 and 0.99 for the extrathoracic region, and from 1.2 to 2.9 for the pulmonary region for 6 species/strain/sex combinations. An RGDR of 1 would indicate no interspecies adjustment.

Response: RGDR values are meaningless without a description of how they were reached, including a description of the mouse and rat toxicity studies (including NOAELs, toxic effects, numbers of hours exposed per day, number of days exposed per week), respiratory parameters, a justification for calling phosphine a category 2 gas (i.e. a transitional gas), and all calculations.

The guidance used in designating effect levels and UFs can be found in the *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA/600/8-90/066F; October 1994). There is no provision for waiving an interspecies UF when using animal data. The Methods document offers the following guidance (page 4-73):

The UFs are generally an order of magnitude, although incorporation of dosimetry adjustments or other mechanistic data has routinely resulted in the use of reduced UFs for RfCs.

The default interspecies UF of 10 includes a pharmacokinetic UF of 3, and a pharmacodynamic UF of 3. Even when a dosimetric adjustment—the regional deposited dose ratio (RDDR) or the regional gas dose ratio (RGDR)—replaces the pharmacokinetic UF, a pharmacodynamic UF of 3 is still used. The interspecies UF would then be the product of 3 (PD component) times the dosimetric adjustment (i.e. >3 but <10). It could be argued that an additional UF should be added to account for the poor quality of the data base, so a total UF of 100 is actually quite liberal.

Acute Reference Exposure (ARE) and Benchmark Dosing

Issue: Acute Reference Exposure (ARE) values were calculated using NOAELs, benchmark dosing, categorical regression, and an interspecies UF of 1.

Response: The AREs and benchmark dosing are methods not used in the Office of Pesticide Programs (OPP). The Coalition provided no information or calculations to support this proposal. They claimed that the literature are adequate for the development of toxicity values using categorical regression, but failed to provide these data. It is inappropriate to calculate AREs using an interspecies UF of 1.

Conclusion

It is impossible to comment at this juncture on the Coalition's proposals for reducing the interspecies UF since the data, equations, and justifications requested at the April 15, 1999 meeting have not yet been submitted for review. As described at that meeting, the RGDR approach remains the only viable option for lowering, but not eliminating, the interspecies UF. This must not be misconstrued as an endorsement, however, because no data were provided to support this approach. Even if an RGDR adjustment is used, it is not likely to lower the interspecies UF enough to be of any real consequence.

Recommendations from Technology Sciences Group Inc.

In a letter to Mark Hartman (March 23, 1999, attached), Dr. Gary J. Burin of Technology Sciences Group Inc. has stated that, "EPA has established a maximum permissible exposure level for phosphine gas in a manner that is neither appropriate for the method in which phosphine is used nor scientifically sound based upon generally accepted principles of risk assessment." He has proposed three way of raising the maximum permissible exposure level.

Route-to-Route Extrapolation

Issue: Exposures in the animal studies should be converted to daily dose levels, expressed in the widely used and scientifically accepted form of the amount of test substance per unit of body weight per day (mg/kg/day). For example, a two hour exposure to phosphine at 20 ppm is equivalent to a dose level of 1.13 mg/kg/day

Response: While "mg/kg/day" is the widely used and scientifically accepted metric for oral and dermal exposure, it is not the accepted metric for inhalation exposure. Inhalation exposure is always expressed as a concentration (mg/L, mg/m³) because the respiratory tract "dose" is unknown.

The only way an inhalation exposure can be expressed as a "mg/kg/day" dose is by performing route-to-route extrapolation. An extrapolation that does not consider all pharmacokinetic differences between the two routes (absorption, rate of absorption, distribution, metabolism, and elimination) can err by orders of magnitude. Dr. Burin stated that a two hour exposure to phosphine at 20 ppm is equivalent to an oral dose level of 1.13 mg/kg/day. This is true only if there are no pharmacokinetic differences between the oral and inhalation routes for phosphine (highly unlikely). Without a PBPK model, there is no way of verifying the accuracy of his extrapolation. Simplistic inhalation to oral extrapolations usually underestimate the inhalation hazard.

PBPK Modeling

Issue: The approach to risk assessment used by the EPA (direct extrapolation [comparisons] of air concentrations in a rodent study to air concentrations for humans) should be used as a first approximation of risk only. It is the total delivered dose to the target tissue that is critical in a risk assessment such as this one, rather than the concentration of the test substance at the interface of the organism and the media. This is accomplished with PBPK modeling.

Response: There is no denying the value of PBPK modeling in route-to-route extrapolations. Indeed, a route-to-route extrapolation can only be considered reasonably reliable if it is based on a complete and accurate PBPK model. The problem with PBPK modeling is that we have never had, and are not likely to have in the foreseeable future, PBPK modeling for any pesticide, including phosphine. This is an unrealistic and unnecessary option. Risk assessments are routinely performed using RfDs, RfCs, MOEs, and Hazard Quotients without PBPK models.

The reason inhalation is always expressed as a concentration (i.e. mg/L) is that we have no way of knowing the animal or human respiratory tract dose, much less the target tissue dose. This is why inhaled chemicals have reference concentrations (RfCs) rather than oral reference doses (RfDs).

A route-specific oral MOE is calculated by dividing an oral NOAEL (in mg/kg) by an oral human exposure (also in mg/kg). Similarly, a route-specific inhalation MOE is calculated by dividing an inhalation NOAEL (in mg/L) by an inhalation exposure (also in mg/L). A route-specific MOE is not corrupted by route-to-route extrapolations. A route-specific inhalation MOE is not a "first approximation of risk," but rather the only accurate and defensible way to calculate inhalation risk.

Fortunately, there is no need to resort to complex and erroneous route-to-route extrapolation and PBPK models. Scientifically valid route-specific MOEs can be calculated for phosphine gas.

Reduction of the 10-Fold Intraspecies Uncertainty Factor

Issue: The 10-fold intraspecies uncertainty factor is designed to protect infants, children, the sick and the elderly. The workplace exposure standard of the RED applies to a generally healthy population of adults. A three-fold intraspecies uncertainty factor should be sufficient in this case. This would result in an acceptable air concentration of 0.6 ppm.

Response: Lowering the intraspecies UF to 3 would result in an acceptable air concentration of 0.1 ppm ($3 \text{ ppm} \div 30 = 0.1 \text{ ppm}$), not 0.6 ppm.

There is no precedent for reducing the intraspecies UF. Of the 5 UF categories, the intraspecies UF is the only one that is always 10. The intraspecies UF of 10 accounts for differences in sensitivity, mass (children, obesity), concomitant exposures, and activity pattern. It does not account for idiosyncracies (Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry; EPA/600/8-90/066F; October 1994; page 4-77). It is not designed to protect every human.

Laboratory rodents are homogeneous, but humans are not. Even among "healthy" adults, there is considerable variation in chemical susceptibility. "Healthy" adults vary considerably in height and weight. A high percentage of the population has some degree of asthma. Los Angeles residents have a 10% reduction in lung function due to smog. It is not unusual for employees to work when they are sick. A female worker may not know she is pregnant. A worker may be unaware of an underlying condition (e.g. kidney or liver damage, neurologic damage, compromised immune system, etc.). Exposure to alcohol, tobacco, and industrial chemicals can profoundly affect health. An adult who smokes or drinks may be more sensitive to a pesticide than a child. Unless all fumigators are Olympic athletes, there is no basis for reducing the intraspecies UF.

Conclusions

With regards to phosphine, Dr. Burin favors inhalation exposures expressed as oral equivalent doses (mg/kg/day), the mandatory use of route-to-route extrapolations, and PBPK models (which we do not have); and opposes the use of route-specific MOEs (except as a “first approximation of risk”) and the full 10-fold intraspecies UF. His positions all run contrary to accepted toxicology and risk assessment practice, the guidance of the Scientific Advisory Panel (SAP), and Agency policy. There is nothing so unique about phosphine that would justify deviating from accepted regulatory practice.