Use of Human Data in Perchlorate Risk Assessment

Comments Submitted by

Toxicology Excellence for
Risk Assessment

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Executive Summary: Key Findings Presented in these Comments

- Overall, we disagree with EPA's conclusions regarding the quality of the human data. EPA misinterpreted epidemiological and statistical data and included unsupported speculations regarding sources of potential confounding, leading to minimal use of important data.

- The perchlorate human database is stronger than many on IRIS, as evidenced by estimations of overall confidence, size of uncertainty factor, and types of available data. US EPA's proposed perchlorate RfD based on animal data suggests that perchlorate is more toxic than several known human toxicants, including methylmercury. However, these conclusions are not supported by the human data, which consistently show no effect associated with perchlorate exposure.

- EPA's human data policy should not be applied to prevent use of clinical studies in designating a NOAEL for perchlorate because: the perchlorate assessment is a scientific assessment rather than a regulatory decision, the Greer study is not a "third-party" study since EPA was intimately involved with the design of the study, and the EPA used the Greer study in the PBPK models.

- The Greer study does not raise ethical concerns posed by EPA's human data policy because it meets the three major requirements of the Common Rule -- review and approval by an Institutional Review Board (IRB), informed consent, and written assurance by government agencies of compliance with Common Rule requirements.

- A thorough QA/QC audit conducted on the Greer study showed no findings that would prevent the Greer study from being used for risk assessment purposes. The response to the TRS audit report demonstrates the study investigators intimate familiarity with the key aspects of this study, suggesting that the study was well-managed overall, even though a number of errors, omissions, and protocol deviations occurred.

Introduction

A primary point for discussion regarding EPA's risk assessment for perchlorate is the choice to base the risk assessment on the animal data. In our opinion, EPA erred in discounting the quality of the epidemiological, clinical, and occupational studies conducted on perchlorate (Appendix A). The quality of the body of human data is equal to or better than that used in many other RfDs based on human data. And for perchlorate, dramatic differences in the response of rats and humans to inhibition of iodine uptake (*TERA*, 2002) suggests that using animal data as the basis of the risk assessment will introduce an unnecessary degree of uncertainty that can be reduced by relying on the human data.

We understand that the EPA has adopted an interim policy on the use of human data and has postponed conclusions regarding the use of human data for the perchlorate risk assessment until the NAS provides a report and recommendation on this issue. We further understand that the EPA does not intend to use this forum to address this issue. We assert, however, that it is not possible to adequately address a risk assessment for perchlorate without taking into account the considerable human clinical data. When the policy is clarified by the NAS or future EPA decisions, the assessment will have to be re-evaluated in light of all of the data.

Therefore, these comments address the following issues:

- Historical use of human data by EPA and evaluation of the quality of the perchlorate human data compared to other human-data based RfDs
- Assessment of why the human clinical data does not fit within EPA's human data policy
- Compliance of the key clinical study with the Common Rule requirements
- QA/QC audit of the key clinical study

Historical Use of Human Data by EPA

EPA's policy when developing RfDs in many of its program offices, regional offices, and ORD has been to use human data first and foremost in the determination of critical effect and choice of uncertainty factors. Because of this policy, EPA risk assessment guidelines and guidance documents have consistently supported the preferred use of adequate human data over that from laboratory animal data in the estimation of risk values such as RfDs (EPA 1989, 1991, 1993, 1998, 1999; Barnes and Dourson, 1988; Dourson, 1994) and RfCs (EPA, 1994; Jarabek, 1994, 1995). This preference for human data can also be found in methods texts of other countries, such as Canada (Meek et al., 1994) and The Netherlands (Rademaker and Linders, 1994), international groups such as the International Programme on Chemical Safety (IPCS, 1994; Meek et al., 2001), other U.S. government organizations such as the Agency for Toxic Substances and Disease Registry (ATSDR, Pohl and Abadin, 1995) and the Food and Drug Administration, and independent groups (e.g., Dourson et al., 2001).

Strength of the Perchlorate Database Compared with Human-Based RfDs

We compared the human database for perchlorate with those of other RfDs based on human data from US EPA's Integrated Risk Information System (IRIS). We find that the perchlorate human database is stronger than many on IRIS, as evidenced by estimations of overall confidence, size

of uncertainty factor, and types of available data. Furthermore, we find that US EPA's proposed perchlorate RfD based on animal data suggests that it is more toxic than aldicarb (30-fold more toxic), arsenic (10-fold more toxic), methyl mercury (3-fold more toxic), and warfarin (10-fold more toxic).

Table 1 shows a comparison of the perchlorate database of human studies in relationship to other RfDs base on human data found on EPA's IRIS. Three points of comparison are shown. The first comparison is that of available human data, listed in Table 1 as clinical, epidemiology, and occupational. A second point of comparison is the size of the uncertainty factor. A third point of comparison is the size of confidence levels. These latter two comparisons, however, depend on a judgment by us that the overall uncertainty factor for perchlorate of 3-fold with these human data is appropriate, and that the confidence in the RfD for perchlorate based on human data is high. EPA judges the overall uncertainty factor based on animal data to be 300, and the overall confidence in the perchlorate RfD to be medium.

A comparison of the available human data of various types for the RfDs shows that perchlorate has human data in all three categories: clinical, epidemiology, and occupational. This is perhaps not surprising for a chemical that is both a drug and an environmental contaminant. This same amount of data is found for only one other human-based RfD, that is barium. In contrast, 23 other human-based RfDs on IRIS have fewer available types of studies.

A comparison of uncertainty factors in the various RfDs shows that a proposed human-based RfD for perchlorate (*TERA*, 2002)[1] has the same uncertainty factor as five other human-based RfDs; uncertainty factors for five other human-based RfDs are lower; uncertainty factors for 14 human-based RfDs are higher. A comparison of confidence levels in the various RfDs shows that the perchlorate has the same high confidence rating as 7 other human-based RfDs: cadmium, fluorine, methyl mercury, nitrate, nitrite, primiphos methyl, and selenium and compounds. The perchlorate RfD has a higher confidence rating than 17 other human-based RfDs.

Comparison of the Value of EPA's Proposed Perchlorate RfD to Human-Based RfDs

How does EPA's proposed RfD for perchlorate of 3 E-5 mg/kg-day compare with RfDs of other chemicals on IRIS? Our findings show that EPA's proposed RfD is lower than any other human based RfD on IRIS, including aldicarb, where the proposed perchlorate RfD is 30-fold lower, arsenic, where it is 10-fold lower, and methyl mercury where it is 3-fold lower. Table 2 shows these results. In fact, EPA's proposed RfD for perchlorate is lower than all but 9 chemicals on IRIS, only being exceeded in toxicity by aroclor 1254, EPN, heptachlor epoxide, sodium fuloroacetate, tetra ethyl lead, and white phosphorus as shown in Table 3.

[1] Based on a 20% BMDL for iodine uptake inhibition from Greer, 2002 and an uncertainty factor of 3 for intraspecies variability.

Table 1. Comparison of Perchlorate Human Database with EPA's RfDs On IRIS As Of May 2000.[2]

Chemical (as on IRIS)	Clinical	Epidemiology	Occupation	Study type for RfD	UF	RfD	RfD Confidence
Aldicarb	v	v		Human experimental gavage	10	1 E-3	Medium
Arsenic, inorganic		v		Human epidemio-logy drinking water	3	3 E-4	Medium
Barium	v	v	v	Human experiment, epidemio-logical drinking water	3	7 E-2	Medium
Baygon	v			Human experimental single dose	100	4 E-3	Medium
Benzoic acid	v	v		Human anecdotal dietary exposure	1	4 E+0	Medium
Cadmium		v	v	Human chronic exposures from a variety of studies	10	5 E-4	High
Chlorpyrifos	v			Human experimental capsule	10	3 E-3	Medium
4,6-Dinitro-o-cyclohexyl phenol	v			Human anecdotal clinical therapy	1000	2 E-3	Low
2,4-Dinitrophenol	v			Human anecdotal clinical therapy	1000	2 E-3	Low
Ethephon	v			Human experimental oral exposure	100	5 E-3	Low
Ethion	v			Human experimental short term	100	5 E-4	Medium
Fluorine (soluble fluoride)		v		Human epidemiology	1	6 E-2	High
Malathion	v			Human experimental feeding	10	2 E-2	Medium
Manganese		v		Human data of several types	1	1.4 E-3	Medium
Methylmercury		v		Human epidemio-logical poisoning	10	1 E-4	High

[2] Availability of data is defined as studies described in EPA's IRIS RfD file only. Some chemicals are known to have other data for the inhalation route (e.g., manganese).

Chemical (as on IRIS)	Clinical	Epidemiology	Occupation	Study type for RfD	UF	RfD	RfD Confidence
Molybdenum	v	v		Human epidemiological dietary	30	5 E-3	Medium
Nitrate	v	v		Human epidemiology surveys	1	1.6 E+0	High
Nitrite	v	v		Human epidemio-logy surveys	1	1 E-1	High
Perchlorate	**v**	**v**	**v**	**Epidemio-logy Study**	**3**	**2 E-3**	**High[3]**
Pirimiphos-methyl	v			Human 56 day experimental feeding	25	1 E-2	High
Selenium and Compounds		v		Human food and soil epidemiology	3	5 E-3	High
Silver		v		Human anecdotal studies	3	5E-3	Low
1,1,2-Trichloro-1,2,2-trifluoroethane	v		v	Human occupation exposure	10	3E+1	Low
Warfarin	v	v		Human experimental	100	3E-4	Low
Zinc and Compounds	v			Human experimental	3	3E-1	Medium

Table 2. Ratio Of IRIS Human Data RfD To EPA's Proposed Perchlorate Rat Based RfD[3].

IRIS RfD	Type of Human Study	Ratio[4]
Aldicarb	experimental gavage	30
Arsenic, inorganic	epidemiology drinking water	10
Barium	experimental, epidemiological drinking water	2000
Baygon	experimental single dose	100
Benzoic acid	anecdotal dietary exposure	100,000
Cadmium	chronic exposures from a variety of studies	20
Chlorpyrifos	experimental capsule	100
Dinitro-o-cyclohexyl phenol	anecdotal clinical therapy	70
2,4-Dinitrophenol	anecdotal clinical therapy	200
Ethephon	experimental oral exposure	200
Ethion	experimental short term	20
Fluorine (soluble fluoride)	epidemiology	2000
Malathion	experimental feeding	700
Manganese	data of several types	50
Methylmercury	epidemiological poisoning	3
Molybdenum	epidemiological dietary	200
Nitrate	epidemiology surveys	50,000
Nitrite	epidemiology surveys	3000
Perchlorate[5]	epidemiology study	70
Pirimiphos-methyl	56 day experimental feeding	300
Selenium and Compounds	food and soil epidemiology	200
Silver	anecdotal studies	200
Trichlorotrifluoroethane	occupational exposure	100,000
Warfarin	experimental	10
Zinc and Compounds	experimental diet supplement	10,000

[3] Of 0.00003 mg/kg-day from EPA, 2002

[4] Ratio determined by dividing the IRIS RfD by the proposed perchlorate RfD. The value can be interpreted as how much more toxic perchlorate is than the given chemical on a chronic basis.

[5] As Per Toxicology Excellence For Risk Assessment (*v. infra*)

Table 3. RfDs on IRIS with values equal to or lower than that proposed by EPA for perchlorate.

Chemical	Value of the RfD (mg/kg-day)
Aldrin	3x10-5
Aroclor 1254	2x10-5
Ethyl p-nitrophenyl phenylphosphorothioate (EPN)	1x10-5
Heptachlor epoxide	1.3x10-5
Merphos	3x10-5
Merphos oxide	3x10-5
Sodium fluoroacetate	2x10-5
Tetraethyl lead	1x10-7
White phosphorus	2x10-5

Human Data Policy

On December 14, 2001 EPA (U.S. EPA, 2001) released its interim policy on the use of third-party studies submitted by regulated entities, and stated its intentions for the National Academy of Sciences to review this policy. The third-party studies that will be the focus of the Academy review are those that have not been conducted or funded by a federal agency in compliance with EPA's Common Rule, or its equivalent. In its press release, EPA indicated "Our paramount concern in developing our policy on these studies must be protection of human health and adherence to the most rigorous ethical and scientific standards." … "During the Academy's consideration of the issues and until a policy is in place, the Agency will not consider or rely on any such human studies in its regulatory decision making, whether previously or newly submitted."

EPA's perchlorate risk assessment cites this policy as one reason why the human database is not adequately considered in the development of the RfD. However, it is inappropriate to apply this policy in the risk assessment for perchlorate for the following reasons:

- This is not a regulatory decision, it is a scientific assessment. As such it should consider any valid scientific studies that are available. Policies relating to regulatory action should be applied at the appropriate regulatory stage.

- The primary clinical study (Greer et al., 2002) was not a 'third party study' as intended in the policy. The study was designed over a period of one year in discussions among the EPA, DOD, and the Principal Investigator and sponsor. Its design accounted for the needs of the DOD for kinetic data for modeling, the PI and lab design constraints and the EPA's specific needs for the risk assessment. The role of the sponsor was simply to fund and monitor the study and to provide the data to EPA so this study should not be considered to be a third part study according to the policy.

- The EPA policy was stimulated by concern about human subject in studies of new pesticides, i.e., relatively unstudied compounds, and the potential unknown risks of exposure. In contrast, perchlorate is a well-understood chemical with a well-known mode of action on the thyroid. The Greer study is primarily looking at inhibition of iodine uptake in euthyroid, iodine sufficient subjects. Inhibition of iodine uptake for a short time is not considered an adverse effect in normal people; it is an early precursor of effects. The highest perchlorate dose used in the study was almost 1000 times lower than the dose that is currently prescribed for amiodorone induced thyrotoxicosis.

- The data from the Greer study is used by EPA in the development of the human PBPK model. If the data can be used for kinetic analysis, it should also be used to understand potential effects.

- Moreover, the study was conducted at the Oregon Health Sciences University (OHSU), an institution that conducts clinical studies using federal funds. OHSU had a Multiple

Project Assurance, issued by the federal Office for Human Research Protection (OHRP), during the time of the Greer study (and since March 2001, has had a Federal-Wide Assurance). These assurances indicate that the OHSU studies are conducted in compliance with the Common Rule.

The basis of the concern about human studies seems to be related to ethical issues. The design and conduct of the Greer study has been evaluated for compliance with the Common Rule, the principles guiding ethical treatment of human studies for the EPA. Moreover, the study was the subject of a rigorous QA/QC audit, which was directed by EPA and was a condition for acceptance of the data or its use in the PBPK modeling by EPA. The results of these two evaluations of the Greer study are presented in the following sections.

Compliance of Greer Study with the Common Rule

TERA evaluated the human study by Dr. Monte Greer (Oregon Health Sciences University), as sponsored by The Perchlorate Study Group, to answer the question "Has this human study met the criteria as established under the Common Rule for the ethical treatment of human subjects?" The Common Rule, as adopted by the US Environmental Protection Agency (EPA), applies only to federally funded research involving human subjects. Note that under current US EPA regulations, this study was not subject to the Common Rule requirements (40 CFR 26).

There are three major requirements of the Common Rule -- review and approval by an Institutional Review Board (IRB), informed consent, and written assurance by government agencies of compliance with Common Rule requirements. This independent evaluation of the Greer human studies has focused on all of these elements in determining whether this study met the requirements of the Common Rule. Note that the third requirement for written assurance is not relevant to this particular study, as The Perchlorate Study Group is not a government agency; however, the Oregon Health Sciences University (OHSU) conducts studies that are federally funded and during the time of this study OHSU had a Multiple Project Assurance (and since March 2001, has had a Federal-Wide Assurance), indicating that OHSU operates in compliance with the Common Rule.

To conduct this review, *TERA* identified key elements of the Common Rule and then examined the Greer study documentation (protocol, IRB approval letter/memorandum, IRB Policy and Procedure Manual, sample consent form, etc.) to determine whether the key elements were addressed. The following summarizes the findings of this review. A more detailed evaluation is found in Appendix B, which identifies the key elements of the Common Rule and the corresponding documentation of the Greer study that indicates compliance with these key elements.

Review and Approval by Institutional Review Board

The protocol and sample consent form for the Greer study were approved by the IRB on February 1, 2000, as evidenced by an approval letter. Additionally, in a Memorandum dated

April 12, 2000, the IRB approved a "Project Revision Amendment" to revise the consent form for the "uptake only" portion of the study. The protocol does not state *per se* that the study was conducted in compliance with the Common Rule; however, a review of the OHSU 2000 Institutional Review Board Policy and Procedure Manual (http://www.ohsu.edu/ra/rso/irb/irbpolicy2000.pdf) and a roster of the IRB from January-June 2000 showed compliance with the Common Rule requirements for IRBs. Additionally, the OHSU 2000 IRB Policy and Procedure Manual was written to ensure compliance with the Common Rule requirements as promulgated by the Department of Health and Human Services (45 CFR 46). For this review, language from the OHSU 2000 IRB Policy and Procedure Manual was compared with the language in the Common Rule as promulgated by EPA (40 CFR 26) and found to be nearly identical. A review of the IRB manual and approval letters provides evidence that this study has met the Common Rule requirement of IRB review and approval (including the requirements of IRB membership, documentation, and procedures).

Written Informed Consent

Based on a review of the protocol, consent form, and TRS quality assurance audit, this study met the requirements of informed consent under the Common Rule. The protocol (and also the OHSU 2000 IRB Policy and Procedure Manual) specifically stated that the study investigators would obtain written informed consent from each subject prior to commencing the study. This was verified in the TRS quality assurance audit (i.e., the Protocol Requirements Spreadsheets and Notes). The audit indicated that each subject had signed a consent form. It also noted that two of the original consent forms were lost, so these consent forms were resigned by the subjects after study completion. A review of the consent form approved by the IRB indicates that the Common Rule requirements for informed consent were followed. For example, the consent form was written in understandable language; it explained the purpose, procedures and duration of research; it contained information about risks/benefits of the research, costs and compensation to subject, confidentiality of records, contact information for questions, consequences of early withdrawal from study, and legal rights. Most importantly, the consent form specifically stated that participation "is completely voluntary" and that the subjects "are free to choose not to serve as a research subject…for any reason." The protocol stated that, "To further assure informed consent, at the Preliminary Visit all potential volunteers will be asked to take home the materials provided and to phone the next day with their decisions concerning participation. Informed consent will be documented by having the volunteer sign the consent form in front of the principal investigator." Based on this information, this study meets the Common Rule requirement of informed consent.

Written Assurance

Although the requirement for written assurance by government agencies is not relevant to this particular study, the attached letter (dated February 14, 2002, See Appendix B) to *TERA* from the Manager of Research Compliance and Assurance at OHSU states that "OHSU conducts all research according to the terms of our federal assurance." The letter also states that during the time of this study, "OHSU operated under a Multiple Project Assurance [MPA] (M1359)" and indicated that the IRB at the time of the study was "constituted according to the requirements of 45 CFR 46." Additionally, the OHSU 2000 IRB Policy and Procedure Manual states, "The

federal Office for Human Research Protection (OHRP) notified OHSU on May 29, 1996 that the MPA had been approved. The new MPA became effective June 1, 1996 and extends for five years" (chapter 1, page 1). The MPA details OHSU's efforts to comply with federal requirements. Thus during the time of this study, OHSU was operating under a MPA and therefore, met the written assurance requirement of the Common Rule even though it was not a requirement for this particular study.

QA/QC Audit of Greer Study

EPA required that the Greer study undergo a rigorous QA/QC audit as a condition for acceptance of the data or its use in the PBPK modeling. The QA/QC audit was conducted by Toxicology/Regulatory Services, Inc. (TRS), who submitted a final audit report to Department of Defense and the Principal Investigator on April 11, 2001. The principal investigator and the DOD addressed deficiencies identified in the audit report; DOD submitted a consultative letter addressing the audit on May 10, 2001. The TRS audit report and DOD consultative letter can be found on EPA's data CD as document ID# 98977. A summary of the TRS audit procedure is presented in Appendix B.

Comments below on the TRS audit report of the Greer human study, together with the study investigators' responses to it, were reviewed by *TERA* staff member Daniel W. Briggs, R.Ph., Ph.D., DABT. Dr. Briggs joined *TERA* as a Visiting Scientist in the fall of 2001 after devoting over 25 years as a toxicologist and manager of product safety for the Procter & Gamble Company. Dr. Briggs has designed and conducted human clinical studies on a variety of personal care products and their ingredients, using both contract laboratories and university facilities, and he is experienced in monitoring and auditing these types of studies.

TRS, Inc. has done a thorough job evaluating a number of different areas of the Greer perchlorate pharmacokinetics and iodine uptake study. Their audit includes an assessment of the study's compliance with protocol requirements and the adequacy of supporting documentation, plus reviews of the data that were collected on thyroid function; on serum and urinary iodine levels; and serum chemistry, hematology, and urinalysis values.

The audit report identifies issues in all of the areas that were evaluated. The types of errors, omissions, and protocol deviations listed in the audit report are those that occur commonly in human clinical studies. This is especially true when the clinical studies are conducted in university settings where staff personnel generally receive little training in the requirements of Good Clinical Practices and are oriented more towards scientific research than regulatory compliance and strict adherence to documentation requirements.

Many of the findings emphasized in the audit relate to the absence or inconsistency of available documentation related to sample collections. Difficulties in obtaining raw data records to verify sample identities and sample collection times also were listed as notable shortcomings of the study. In addition, some of the documentation provided to TRS was in the form of Excel spreadsheets, raising concerns of data recording and storage vulnerabilities because of possibilities that the spreadsheets may have undergone alterations without proper tracking and documentation of changes. Subsequently, these issues were addressed and largely negated when

the investigators clarified the procedures used to transfer raw data from sample labels and lab slips to a Paradox database. The Excel spreadsheets were not used for data storage but were prepared at a later date from the Paradox database for the sole purpose of meeting the auditor's requests for information.

Other findings in the audit report describe omissions of sample analyses, recording errors, and discrepancies between the protocol and the study execution. In some cases, further explanation and clarification from the investigators resolved these issues; in other cases measures were taken to correct confirmed documentation errors or to perform procedures that were mistakenly omitted. Details describing how the audit findings were addressed are provided in the investigators' point-by-point response to the audit report (Goodman, Previti, and Pino; April 26, 2001). Although some issues identified in the audit report could not be satisfactorily resolved by further explanation or corrective action, none of these remaining items are judged sufficient to invalidate this study or to question its scientific credibility.

In the concluding remarks of its audit report, TRS states that the information presented in the perchlorate study, when combined with the subsequent data corrections and additional documentation "may permit a scientific reviewer to conclude that the data from this study are reliable and accurate enough to support the PB/PK modeling project." This conclusion appears to be justified. The explanatory document (referenced above) prepared in response to the TRS audit report demonstrates the study investigators intimate familiarity with the key aspects of this study, suggesting that the study was well-managed overall, even though a number of errors, omissions, and protocol deviations occurred.

No findings were presented in the TRS audit report that would prevent the Greer study from being used for risk assessment purposes.

Conclusion

Overall, we disagree with EPA's conclusions regarding the quality of the human data. The EPA's review of the epidemiology studies reflects some misunderstanding of the biological basis of the neonatal thyroid-screening program, leading to misinterpretation of epidemiological and statistical data. The EPA's review includes unsupported speculations regarding sources of potential confounding that leads to minimal use of important data (Appendix A).

Rather, we find that the perchlorate human database is stronger than many on IRIS, as evidenced by estimations of overall confidence, size of uncertainty factor, and types of available data. Furthermore, we find that US EPA's proposed perchlorate RfD based on animal data suggests that it is more toxic than aldicarb (30-fold more toxic), arsenic (10-fold more toxic), methyl mercury (3-fold more toxic), and warfarin (10-fold more toxic). However, these conclusions are not supported by the human data, which consistently show no effect associated with perchlorate exposure.

We conclude that the Greer study meets the three major requirements of the Common Rule -- review and approval by an Institutional Review Board (IRB), informed consent, and written

assurance by government agencies of compliance with Common Rule requirements. A review of the IRB manual and approval letters provides evidence that this study has met the Common Rule requirement of IRB review and approval (including the requirements of IRB membership, documentation, and procedures). Based on a review of the protocol, consent form, and TRS quality assurance audit, this study met the requirements of informed consent under the Common Rule. During the time of this study, "OHSU operated under a Multiple Project Assurance [MPA] (M1359)" and indicated that the IRB at the time of the study was "constituted according to the requirements of 45 CFR 46" and therefore, met the written assurance requirement of the Common Rule even though it was not a requirement for this particular study.

Finally, a thorough QA/QC audit was conducted on the Greer study. No findings were presented in the TRS audit report that would prevent the Greer study from being used for risk assessment purposes. The response to the TRS audit report demonstrates the study investigators intimate familiarity with the key aspects of this study, suggesting that the study was well-managed overall, even though a number of errors, omissions, and protocol deviations occurred.

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